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(71) Applicant (for all designated States except US): ANTI-SOMA RESEARCH LIMITED [GB/GB]; West Africa House, Hanger Lane, Ealing, London W5 3QR (GB).

(72) Inventor; and

(75) Inventor/Applicant (for US only): YOUNG, Robert, James [GB/GB]; Antisoma Research Limited, West Africa House, Hanger Lane, Ealing, London W5 3QR (GB).

(74) Agent: THOMAS, Philip, J., D.; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

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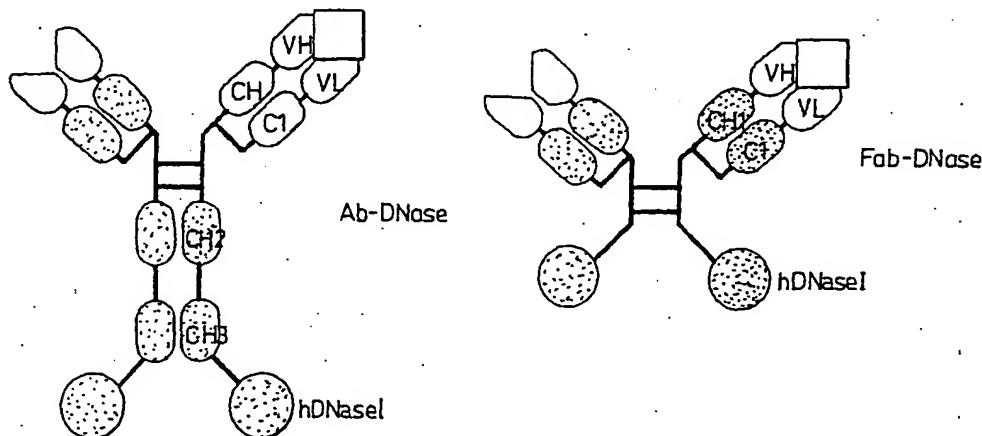
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(54) Title: COMPOUNDS FOR TARGETING



(57) Abstract: A compound comprising a target cell-specific portion and a cytotoxic portion characterised in that the target cell-specific portion comprises a humanised monoclonal antibody having specificity for polymorphic epithelial mucin (PEM), or an antigen binding fragment thereof, and the cytotoxic portion has endonucleolytic activity. Preferably, the target cell-specific portion comprises a humanised HMFG-1 antibody or an antigen binding fragment thereof. Advantageously, the cytotoxic portion is at least the catalytically active portion of a DNA endonuclease, e.g. a human DNA endonuclease I. The invention further provides nucleic acids encoding the compounds of the invention, and the use of such compounds in medicine, e.g. in the treatment of cancer.

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COMPOUNDS FOR TARGETING

The present invention relates to cytotoxic compounds that have a high
5 avidity for, and can be targeted to, selected cells. Specifically, the
invention provides compounds comprising a cytotoxic portion having
DNA endonucleolytic activity and a target-cell specific portion having
specificity for human polymorphic epithelial mucin (PEM).

10 Background

The cell-specific targeting of compounds that are directly, or indirectly,
cytotoxic has been proposed as a way to combat diseases such as cancer.
Bagshawe and his co-workers have disclosed (Bagshawe (1987) *Br. J.*
15 *Cancer* 56, 531; Bagshawe *et al* (1988) *Br. J. Cancer* 58, 700; WO
88/07378) conjugated compounds comprising an antibody or part thereof
and an enzyme, the antibody being specific to tumour cell antigens and the
enzyme acting to convert an innocuous pro-drug into a cytotoxic
compound. The cytotoxic compounds were alkylating agents, *e.g.* a
20 benzoic acid mustard released from *para*-N-bis(2-
chloroethyl)aminobenzoyl glutamic acid by the action of *Pseudomonas sp.*
CPG2 enzyme.

An alternative system using different pro-drugs has been disclosed
25 (WO 91/11201) by Epenetos and co-workers. The cytotoxic compounds
were cyanogenic monosaccharides or disaccharides, such as the plant
compound amygdalin, which release cyanide upon the action of a β -
glucosidase and hydroxynitrile lyase.

In a further alternative system, the use of antibody-enzyme conjugates containing the enzyme alkaline phosphatase in conjunction with the pro-drug etoposide 4'-phosphate or 7-(2'-aminoethyl phosphate)mitomycin or
5 a combination thereof have been disclosed (EP 0 302 473; Senter *et al* (1988) *Proc. Natl. Acad. Sci. USA* 85, 4842).

Rybak and co-workers have disclosed (Rybak *et al* (1991) *J. Biol. Chem.* 266, 21202; WO 91/16069) the cytotoxic potential of a monomeric
10 pancreatic ribonuclease when injected directly into *Xenopus* oocytes and the cytotoxic potential of monomeric RNase coupled to human transferrin or antibodies directed against the transferrin receptor. The monomeric RNase hybrid proteins were cytotoxic to human erythroleukaemia cells *in vitro*.

15 Other approaches are the *in vivo* application of streptavidin conjugated antibodies followed, after an appropriate period, by radioactive biotin (Hnatowich *et al* (1988) *J. Nucl. Med.* 29, 1428-1434), or injection of a biotinylated mAb followed by radioactive streptavidin (Paganelli *et al*
20 (1990) *Int. J. Cancer* 45, 1184-1189). A pilot radioimmunolocalisation study in non-small cell lung carcinomas was conducted with encouraging results (Kalofonos *et al* (1990) *J. Nucl. Med.* 31, 1791-1796).

Apart from these examples, it is rather more common to see biotinylated
25 antibodies and streptavidin-enzyme conjugates, which are used in enzyme-linked immunosorbent assays.

These previous systems have used relatively large antibody-enzyme,

antibody-streptavidin or antibody-biotin conjugates and may comprise portions of non-mammalian origin which are highly immunoreactive.

We have now devised improved compounds for targeting cells to be
5 destroyed.

Summary of Invention

A first aspect of the invention provides a compound comprising a target
10 cell-specific portion and a cytotoxic portion characterised in that the target cell-specific portion comprises an humanised monoclonal antibody having specificity for polymorphic epithelial mucin (PEM), or an antigen binding fragment thereof, and the cytotoxic portion has endonucleolytic activity.

15 By "target cell specific" portion we mean the portion of the compound which comprises one or more binding sites which recognise and bind to polymorphic epithelial mucin (PEM) on the target cell. Upon contact with the target cell, the target cell specific portion is preferably internalised along with the cytotoxic portion. Such internalisation results in the
20 cytotoxic portion being delivered to the cell cytosol, where it has access to the cell's nucleic acid molecules.

The target cell-specific portion of the compounds of the invention comprises an humanised monoclonal antibody having specificity for
25 polymorphic epithelial mucin (PEM), or an antigen binding fragment thereof.

Polymorphic epithelial mucin, or PEM, is a component of the human milk

fat globule. PEM is expressed by cells in several body tissues and is also found in urine. Significantly, PEM is known to be expressed in epithelial cancer cells, notably in ovarian, gastric, colorectal and pancreatic cancer cells.

5

Monoclonal antibodies which will bind to PEM are already known, but in any case, with today's techniques in relation to monoclonal antibody technology, antibodies can be prepared to most antigens. The antigen-specific portion may be a whole antibody, a part of an antibody (for
10 example a Fab or F(ab')₂ fragment), a synthetic antibody fragment (for example a single chain Fv fragment [ScFv]), or a peptide/peptidomimetic or similar. Suitable monoclonal antibodies to selected antigens may be prepared by known techniques, for example those disclosed in
15 *"Monoclonal Antibodies: A manual of techniques"*, H Zola (CRC Press, 1988) and in *"Monoclonal Hybridoma Antibodies: Techniques and Applications"*, J G R Hurrell (CRC Press, 1982) and *Antibody Engineering, A Practical Approach*, McCafferty, J. et al, ed. (IRL Pres, 1996).

20 By 'humanised monoclonal antibody' we include monoclonal antibodies having at least one chain wherein the framework regions are predominantly derived from a first, acceptor monoclonal antibody of human origin and at least one complementarity-determining region (CDR) is derived from a second, donor monoclonal antibody having specificity
25 for PEM. The donor monoclonal antibody may be of human or non-human origin, for example it may be a murine monoclonal antibody.

Preferably, both chains of the humanised monoclonal antibody comprise

CDRs grafted from a donor monoclonal antibody having specificity for PEM.

Advantageously, the CDR-grafted (*i.e.* humanised) chain comprises two
5 or all three CDRs derived from a donor antibody having specificity for PEM.

Conveniently, the humanised monoclonal antibody comprises only human
framework residues and CDRs from a donor antibody having specificity
10 for PEM.

However, it will be appreciated by those skilled in the art that in order to
maintain and optimise the specificity of the humanised antibody it may be
necessary to alter one or more residues in the framework regions such that
15 they correspond to equivalent residues in the donor antibody.

Conveniently, the framework regions of the humanised antibody are
derived from an human IgG monoclonal antibody.

20 Methods of making humanised monoclonal antibodies are well-known in
the art, for example see Jones *et al.* (1986) *Nature* 321:522-525,
Riechmann *et al.* (1988) *Nature* 332:323-327, Verhoeyen *et al.* (1988)
Science 239:1534-1536 and EP 239 400 (to Winter).

25 In a preferred embodiment of the first aspect of the invention, the target
cell-specific portion comprises an humanised HMFG-1 monoclonal
antibody or an antigen binding fragment thereof.

HMFG antibodies are raised against human milk fat globule (HMFG), in a delipidated state (see Taylor-Papadimitriou *et al.*, 1981, *Int. J. Cancer* 28:17-21 and Gendler *et al.*, 1988, *J. Biol. Chem.* 236:1282-12823).

HMFG-1 monoclonal antibodies bind to a particular component of
5 HMFG, namely polymorphic epithelial mucin (PEM). Binding is thought to involve the amino acid sequence APDTR within the twenty amino acid tandem repeats of the *muc-1* gene product.

Exemplary humanised HMFG-1 antibodies are disclosed in WO 92/04380.

10

Advantageously, the target cell-specific portion is an humanised HMFG-1 monoclonal antibody.

In a preferred embodiment of the first aspect of the invention, the target
15 cell-specific portion comprises a fragment of an humanised monoclonal antibody having specificity for polymorphic epithelial mucin (PEM), said fragment retaining the antigen binding properties of the parent antibody.

The variable heavy (V_H) and variable light (V_L) domains of the antibody
20 are involved in antigen recognition, a fact first recognised by early protease digestion experiments. Further confirmation was found by "humanisation" of rodent antibodies. Variable domains of rodent origin may be fused to constant domains of human origin such that the resultant antibody retains the antigenic specificity of the rodent parented antibody
25 (Morrison *et al* (1984) *Proc. Natl. Acad. Sci. USA* 81, 6851-6855).

That antigenic specificity is conferred by variable domains and is independent of the constant domains is known from experiments involving

the bacterial expression of antibody fragments, all containing one or more variable domains. These molecules include Fab-like molecules (Better *et al* (1988) *Science* 240, 1041); Fv molecules (Skerra *et al* (1988) *Science* 240, 1038); disulphide-linked Fv molecules (Young *et al.*, 1995, *FEBS Lett.* 377:135-139); single-chain Fv (ScFv) molecules where the V_H and V_L partner domains are linked via a flexible oligopeptide (Bird *et al* (1988) *Science* 242, 423; Huston *et al* (1988) *Proc. Natl. Acad. Sci. USA* 85, 5879) and single domain antibodies (dAbs) comprising isolated V domains (Ward *et al* (1989) *Nature* 341, 544). A general review of the techniques involved in the synthesis of antibody fragments which retain their specific binding sites is to be found in Winter & Milstein (1991) *Nature* 349, 293-299.

By "ScFv molecules" we mean molecules wherein the V_H and V_L partner domains are linked via a flexible oligopeptide.

Chimaeric antibodies are discussed by Neuberger *et al* (1988, 8th *International Biotechnology Symposium Part 2*, 792-799).

The advantages of using antibody fragments, rather than whole antibodies, are several-fold. The smaller size of the fragments allows for rapid clearance, and may lead to improved tumour to non-tumour ratios. Fab, Fv, ScFv, disulphide Fv and dAb antibody fragments can all be expressed in and secreted from bacteria, such as *E. coli*, or eukaryotic expression systems such as Yeast or mammalian systems, thus allowing the facile production of large amounts of the said fragments.

Whole antibodies, and F(ab')₂ fragments are "bivalent". By "bivalent" we

mean that the said antibodies and $F(ab')_2$ fragments have two antigen combining sites. In contrast, Fab, Fv, ScFv, disulphide Fv and dAb fragments are monovalent, having only one antigen combining site.

- 5 Preferably, the target cell-specific portion of the compounds of the invention comprises an antigen binding fragment of the humanised antibody selected from the group consisting of Fab-like molecules, such as Fab and $F(ab')_2$, Fv molecules, disulphide-linked Fv molecules, ScFv molecules and single domain antibodies (dAbs).

10

More preferably, the target cell-specific portion comprises a Fab molecule or a $F(ab')_2$ molecule.

- 15 Yet more preferably, the target cell-specific portion comprises an amino acid sequence encoded by at least part of one or both of the nucleotide sequences of Figure 3(a) and (d).

- Most preferably, the target cell-specific portion comprises an amino acid sequence encoded by the nucleotide sequence of Figure 3(a) and an amino
20 acid sequence encoded by the nucleotide sequence of Figure 3(d).

Preferably, the target cell-specific portion recognises the target cell with high avidity.

- 25 By "high avidity" we mean that the target cell-specific portion recognises the target cell with a binding constant of at least $K_d = 10^{-6}$ M, preferably at least $K_d = 10^{-9}$ M, suitably $K_d = 10^{-10}$ M, more suitably $K_d = 10^{-11}$ M, yet more suitably still $K_d = 10^{-12}$ M, and more preferably $K_d = 10^{-15}$ M or

even $K_d = 10^{-18}$ M.

Preferably, the target cell-specific portion comprises an antigen binding fragment of an humanised HMFG-1 monoclonal antibody, *e.g.* an Fab or
5 F(ab')₂ fragment thereof, wherein a hinge region contains a mutation (*i.e.* wherein the hinge is a variant or hybrid of a naturally occurring hinge). More preferably, the variant hinge comprises the amino acid sequence CCVECPPCPAPE.

10 By 'cytotoxic portion' we mean a portion having endonucleolytic activity which is toxic to the cell if it is to reach, and preferably enter said cell.

In a preferred embodiment of the first aspect of the invention, the cytotoxic portion has DNA endonucleolytic activity.

15

Advantageously, the cytotoxic portion is at least the catalytically active portion of a DNA endonuclease.

Examples of known DNA endonucleases include bovine DNase I (see
20 Worrall and Conolly, 1990, *J. Biol. Chem.* 265:21889-21895). Human pancreatic DNase I has also been cloned (see Shak *et al.*, 1990, *Proc. Natl. Acad. Sci. USA* 87:9188-9192 and Hubbard *et al.*, 1992, *New Eng. J. Med.* 326:812-815).

25 Preferably, the endonuclease is a mammalian deoxyribonuclease I.

More preferably, the endonuclease is a human deoxyribonuclease I.

Most preferably, the cytotoxic portion comprises the amino acid sequence shown in Figure 2(a) or 2(b).

Preferably, the cytotoxic portion of the compound of the invention is capable of oligomerisation, *e.g.* dimerisation. Attachment of the target-cell specific portion to a cytotoxic portion capable of oligomerisation provides a method for increasing the number of binding sites to the target cell. For example, if the target cell-specific portion is joined to a portion capable of forming a dimer then the number of target cell-specific binding sites is two; if the target cell-specific portion is joined to a portion capable of forming a tetramer then the number of target cell-specific binding sites is four. The number of target cell-specific binding sites is greater than one and the compounds may therefore have a greater avidity for the target cell than do compounds which only have one target cell-specific binding site.

It is preferable for the cytotoxic portion of the compound of the invention capable of oligomerisation to contain no interchain disulphide bonds nor intrachain disulphide bonds; to be well characterised; to be non-toxic; to be stable; to be amenable to preparation in a form suitable for pre-clinical or clinical use or be in pre-clinical or clinical use; and for the subunit monomers to have a high affinity for each other, that is they contain one or more subunit binding sites.

Advantageously, the cytotoxic portion is of mammalian, preferably human, origin. The use of the said mammalian proteins as the cytotoxic portion of the compound of the invention is advantageous since such compounds are less likely to give rise to undesirable immune reactions.

It will be appreciated by those skilled in the art that the cytotoxic portion may be a variant of a naturally occurring endonuclease.

- 5 By "a variant" we include cytotoxic portions comprising of a naturally occurring endonuclease wherein there have been amino acid insertions, deletions or substitutions, either conservative or non-conservative, such that the changes do not substantially reduce the endonuclease activity of the variant compared to that of the naturally occurring endonuclease. For
10 example, the variant may have increased activity compared to the naturally occurring endonuclease

Such variants may be made using methods of protein engineering and site-directed mutagenesis commonly known in the art (for example, see
15 Sambrook *et al.*, 1989, *Molecular cloning: A Laboratory Manual*, 2nd edition, Cold Spring Harbor Laboratory Press, NY, USA).

- In an alternative embodiment, the endonuclease is a restriction endonuclease, such as a microbial type II restriction endonuclease.
20 Exemplary type II restriction endonucleases include *Bam*HI, *Hind*III, *Msp*I, *Sau*3AI, *Hin*fI, *Not*I and *Eco*RI.

In another preferred embodiment of the first aspect of the invention, a nuclear localization signal is incorporated into the compound.

25

Preferably, the nuclear localization signal (NLS) comprises a nuclear localization signal from the SV40 large T antigen (Kalderon *et al.*, 1984, *Cell* 39:499-509), and specifically the amino acid sequence PKKKRKV.

Inclusion of a nuclear localization signal encourages the compound of the invention to gain access to the chromosomal DNA during the periods of the cell cycle when the nuclear membrane is intact, since the nuclear pores are permeable to large molecules incorporating said nuclear localization
5 signal.

In a further preferred embodiment of the first aspect of the invention, the target cell-specific portion and the cytotoxic portion are fused to create a fusion compound.

10

By "fusion compound" we include a compound comprising one or more functionally distinct portions, wherein the distinct portions are contained within a single polypeptide chain produced by recombinant DNA techniques. For example, the compound may comprise a whole antibody
15 wherein the heavy chain is fused to human DNase I. Alternatively, the compound may comprise an Fab or F(ab')₂ fragment of an antibody wherein the truncated heavy chain (*i.e.* the Fd chain) is fused to human DNase I.

20 Preferably, the target-cell specific and the cytotoxic portion of the fusion compound of the invention separated by a linker sequence, for example to allow greater flexibility of the portions relative to one another.

More preferably, the linker sequence comprises a GG dipeptide.

25

Most preferably the linker sequence is or comprises GG or GSGG.

Alternatively, the target-cell specific and the cytotoxic portion of the

compound of the invention are separate moieties linked together by any of the conventional ways of cross-linking polypeptides, such as those generally described in O'Sullivan *et al Anal. Biochem.* (1979) 100, 100-108. For example, the antibody portion may be enriched with thiol
5 groups and the enzyme portion reacted with a bifunctional agent capable of reacting with those thiol groups, for example the N-hydroxysuccinimide ester of iodoacetic acid (NHIA) or N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP). Amide and thioether bonds, for example achieved with m-maleimidobenzoyl-N-hydroxysuccinimide ester,
10 are generally more stable *in vivo* than disulphide bonds.

In a preferred embodiment of the first aspect of the invention, the compound comprises all or part of the amino acid sequence as shown in Figure 3(c) (*i.e.* an HMFG-1 light chain) together with all or part of an
15 amino acid sequence selected from the group consisting of amino acid sequences as shown in Figures 5(d), 6(d), 7(b), 8(b), 9(b), 10(b), 11(b), 12(b), 13(d), 14(d), 15(d), 16(c), 17(d), 18(d) and 19(d) (*i.e.* an HMFG-1 heavy or Fd chain/DNase fusion).

20 Advantageously, the compound is a whole HMFG-1 antibody/human DNase I fusion compound comprising an amino acid sequence as shown in Figure 3(c) and an amino acid sequence as shown in Figure 7(b). Preferably, the compound is a tetrameric compound comprising two HMFG-1 light chains and two HMFG-1 heavy chain /DNase I fusions.

25 Conveniently, the compound comprises an amino acid sequence as shown in Figure 3(c) and an amino acid sequence as shown in Figure 14(d).

Preferably, the compound comprises one of the pairs of amino acid sequences defined above wherein the leader sequence of each amino acid (the first 19 amino acids of the sequences shown in each figure) is removed. It will be appreciated by persons skilled in the art that the compounds of the invention may also comprise variants of such amino acid sequences.

Suitably, the compound is a tetrameric compound comprising two HMFG-1 light chains and two HMFG-1 Fd chain /DNase I fusions. More preferably, the compound is a dimeric compound comprising one HMFG-1 light chain and one HMFG-1 Fd chain /DNase I fusion.

A second aspect of the invention provides a nucleic acid molecule encoding a compound according to the first aspect of the invention, or a target cell-specific portion or cytotoxic portion thereof.

By "nucleic acid molecule" we include DNA, cDNA and mRNA molecules.

In a preferred embodiment of the second aspect of the invention, the nucleic acid molecule comprises all or part of the nucleotide sequence as shown in Figure 3(a or b) (*i.e.* encoding an HMFG-1 light chain) together with all or part of a nucleotide sequence selected from the group consisting of nucleotide sequences as shown in Figures 5(a, b and c), 6(a, b and c), 7(a), 8(a), 9(a), 10(a), 11(a), 12(a), 13(a, b and c), 14(a, b and c), 15(a, b and c), 16(a and b), 17(a, b and c), 18(a, b and c) and 19(a, b and c) (*i.e.* encoding an HMFG-1 heavy or Fd chain/DNase fusion).

Advantageously, the nucleic acid molecule comprising a nucleotide sequence as shown in Figure 3(b) and a nucleotide sequence as shown in Figure 7(a).

- 5 Conveniently, the compound comprises a nucleotide sequence as shown in Figure 3(b) and a nucleotide sequence as shown in Figure 14(c).

Alternatively, the nucleic acid molecule comprises nucleotide sequences that are degenerate sequences of those nucleotide sequences identified
10 above (*i.e.* which encode the same amino acid sequence).

A further aspect of the present invention provides a method of making a compound according to the first aspect of the invention, said method comprising expressing one or more nucleic acid molecules according to
15 the second aspect of the invention in a host cell and isolating the compound therefrom.

It is preferable that the two portions of the compound of the invention are produced as a fusion compound by recombinant DNA techniques,
20 whereby a length of DNA comprises respective regions encoding the two portions of the compound of the invention either adjacent one another or separated by a region encoding a linker peptide which does not destroy the desired properties of the compound. The benefits in making the compound of the invention using recombinant DNA techniques are several
25 fold. Firstly, it enables a high degree of precision with which the two portions of the compound can be joined together. Secondly, the construction of compounds which are "hetero-oligomeric" can be controlled by the expression of the different recombinant DNA molecules

encoding each of the different type of subunit of the "hetero-oligomer" in the same host cell.

By "hetero-oligomer" we mean those compounds in which two or more
5 different cell-specific portions are joined to either the same or to different subunits which are capable of oligomerisation. The expression, in the same host cell of two compounds, of A and B, each with different target cell specific portions but with a common second portion capable of oligomerisation will result in a mixed population of compounds. For
10 example, if the common second portion is capable of dimerisation, three potential compounds will be produced: A_2 , AB and B_2 , in a ratio of 1:2:1, respectively.

The separation of the desired compound with each of the different cell
15 specific portions, that is AB, can be achieved by two step affinity chromatography.

Application of the mixture of compounds to an affinity column specific for A will result in the binding of A_2 and AB. These compounds are eluted
20 from this first column, and then applied to an affinity column specific for B. This will result in AB, but not A_2 , being bound to the column. Finally, the desired product AB, can be eluted.

Of course, the order in which the affinity columns are used is not
25 important.

The same principle of separating those compounds with two or more different binding sites can be applied to the purification of the desired

compounds from mixtures of other hetero-oligomers.

Conceivably, the two portions of the compound may overlap wholly or partly.

5

Preferably, the compound is a multimeric compound such as a whole antibody/DNase fusion comprising two light chains and two heavy chains (H_2L_2), a $F(ab')_2$ fusion comprising two light chains and two truncated heavy chains (Fd_2L_2), or a Fab fusion comprising one light chain and one

10

truncated heavy chain (FdL).

The nucleic acid may be expressed in a suitable host to produce a polypeptide comprising the compound of the invention. Thus, the nucleic acid encoding the compound of the invention or a portion thereof may be

15 used in accordance with known techniques, appropriately modified in view of the teachings contained herein, to construct an expression vector, which is then used to transform an appropriate host cell for the expression and production of the polypeptide of the invention. Such techniques include those disclosed in US Patent Nos. 4,440,859 issued 3 April 1984 to Rutter

20 *et al*, 4,530,901 issued 23 July 1985 to Weissman, 4,582,800 issued 15 April 1986 to Cowl, 4,677,063 issued 30 June 1987 to Mark *et al*, 4,678,751 issued 7 July 1987 to Goeddel, 4,704,362 issued 3 November 1987 to Itakura *et al*, 4,710,463 issued 1 December 1987 to Murray, 4,757,006 issued 12 July 1988 to Toole, Jr. *et al*, 4,766,075 issued 23

25 August 1988 to Goeddel *et al* and 4,810,648 issued 7 March 1989 to Stalker, all of which are incorporated herein by reference.

Where the compound of the invention is multimeric, the constituent chains

may be encoded by a single nucleic acid molecule or separate nucleic acid molecule (expressed in a common host cell or in different host cells and assembled *in vitro*).

- 5 The nucleic acid encoding the compound of the invention or a portion thereof may be joined to a wide variety of other nucleic acid sequences for introduction into an appropriate host. The companion nucleic acid will depend upon the nature of the host, the manner of the introduction of the nucleic acid into the host, and whether episomal maintenance or
10 integration is desired.

It will be appreciated that in order to prevent expression of the cytotoxic portion of the compound of the invention from killing the host cells in which it is expressed, it may be necessary to link the nucleic acid of the
15 second aspect of the invention to a signal sequence capable of directing secretion of the expressed compound (or portion) out of the host cell. Signal sequences will be selected according to the type of host cell used. Exemplary signal sequences include the *ompA* signal sequence (for example, see Takahara *et al.*, 1985, *J. Biol. Chem.* 260(5):2670-2674).

- 20 Generally, the nucleic acid is inserted into an expression vector, such as a plasmid, in proper orientation and correct reading frame for expression. If necessary, the nucleic acid may be linked to the appropriate transcriptional and translational regulatory control nucleotide sequences
25 recognised by the desired host, although such controls are generally available in the expression vector. For example, the nucleic acid molecule encoding a compound of the invention may be linked to or comprise a Kozak consensus ribosome binding sequence (such as GCCGCCACC) to

enhance translation.

The vector is then introduced into the host through standard techniques.

Generally, not all of the hosts will be transformed by the vector.

- 5 Therefore, it will be necessary to select for transformed host cells. One selection technique involves incorporating into the expression vector a nucleic acid sequence, with any necessary control elements, that codes for a selectable trait in the transformed cell, such as antibiotic resistance. Alternatively, the gene for such selectable trait can be on another vector,
10 which is used to co-transform the desired host cell.

- Host cells that have been transformed by the recombinant nucleic acid of the invention are then cultured for a sufficient time and under appropriate conditions known to those skilled in the art in view of the teachings
15 disclosed herein to permit the expression of the polypeptide, which can then be recovered.

- Many expression systems are known, including bacteria (for example *E. coli* and *Bacillus subtilis*), yeasts (for example *Saccharomyces cerevisiae*
20 and *Pichia pastoris*), filamentous fungi (for example *Aspergillus*), plant cells, animal cells (for example COS-1, COS-7, CHO, NIH 3T3, NS0 and BHK cells) and insect cells (for example *Drosophila*, SF9 cells).

- Those vectors that include a replicon such as a procaryotic replicon can
25 also include an appropriate promoter such as a procaryotic promoter capable of directing the expression (transcription and translation) of the genes in a bacterial host cell, such as *E. coli*, transformed therewith.

A promoter is an expression control element formed by a DNA sequence that permits binding of RNA polymerase and transcription to occur. Promoter sequences compatible with exemplary bacterial hosts are typically provided in plasmid vectors containing convenient restriction
5 sites for insertion of a DNA segment of the present invention.

Typical procaryotic vector plasmids are pUC18, pUC19, pBR322 and pBR329 (available from Biorad Laboratories, Richmond, CA, USA), pTrc99A and pKK223-3 (available from Pharmacia Piscataway, NJ, USA)
10 and the pET system (T7 promoter, Novagen Ltd).

A typical mammalian cell vector plasmid is pSVL available from Pharmacia, Piscataway, NJ, USA. This vector uses the SV40 late promoter to drive expression of cloned genes, the highest level of
15 expression being found in T antigen-producing cells, such as COS-1 cells.

An example of an inducible mammalian expression vector is pMSG, also available from Pharmacia. This vector uses the glucocorticoid-inducible promoter of the mouse mammary tumour virus long terminal repeat to
20 drive expression of the cloned gene.

Useful yeast plasmid vectors are pRS403-406 and pRS413-416 and are generally available from Stratagene Cloning Systems, La Jolla, CA 92037, USA. Plasmids pRS403, pRS404, pRS405 and pRS406 are Yeast
25 Integrating plasmids (YIps) and incorporate the yeast selectable markers *his3*, *trp1*, *leu2* and *ura3*. Plasmids pRS413-416 are Yeast Centromere plasmids (YCps).

Further useful vectors for transformation of yeast cells, such as *Pichia*, include the 2 μ plasmid pYX243 (available from R and D Systems Limited) and the integrating vector pPICZ series (available from Invitrogen).

- 5 A variety of methods have been developed to operatively link DNA to vectors via complementary cohesive termini. For instance, complementary homopolymer tracts can be added to the DNA segment to be inserted to the vector DNA. The vector and DNA segment are then joined by hydrogen bonding between the complementary homopolymeric
10 tails to form recombinant DNA molecules.

Synthetic linkers containing one or more restriction sites provide an alternative method of joining the DNA segment to vectors. The DNA segment, generated by endonuclease restriction digestion as described
15 earlier, is treated with bacteriophage T4 DNA polymerase or *E. coli* DNA polymerase I, enzymes that remove protruding, 3'-single-stranded termini with their 3'-5'-exonucleolytic activities, and fill in recessed 3'-ends with their polymerizing activities.

- 20 The combination of these activities therefore generates blunt-ended DNA segments. The blunt-ended segments are then incubated with a large molar excess of linker molecules in the presence of an enzyme that is able to catalyze the ligation of blunt-ended DNA molecules, such as bacteriophage T4 DNA ligase. Thus, the products of the reaction are
25 DNA segments carrying polymeric linker sequences at their ends. These DNA segments are then cleaved with the appropriate restriction enzyme and ligated to an expression vector that has been cleaved with an enzyme that produces termini compatible with those of the DNA segment.

Synthetic linkers containing a variety of restriction endonuclease sites are commercially available from a number of sources including International Biotechnologies Inc, New Haven, CN, USA.

5

A desirable way to modify the nucleic acid encoding the compound of the invention or a portion thereof is to use the polymerase chain reaction as disclosed by Saiki *et al* (1988) *Science* 239, 487-491.

10 In this method the nucleic acid to be enzymatically amplified is flanked by two specific oligonucleotide primers which themselves become incorporated into the amplified nucleic acid. The said specific primers may contain restriction endonuclease recognition sites which can be used for cloning into expression vectors using methods known in the art.

15

Exemplary genera of yeast contemplated to be useful in the practice of the present invention are *Pichia*, *Saccharomyces*, *Kluyveromyces*, *Candida*, *Torulopsis*, *Hansenula*, *Schizosaccharomyces*, *Citeromyces*, *Pachysolen*, *Debaromyces*, *Metschnikowia*, *Rhodospiridium*, *Leucosporidium*,
20 *Botryosascus*, *Sporidiobolus*, *Endomycopsis*, and the like. Preferred genera are those selected from the group consisting of *Pichia*, *Saccharomyces*, *Kluyveromyces*, *Yarrowia* and *Hansenula*. Examples of *Saccharomyces* are *Saccharomyces cerevisiae*, *Saccharomyces italicus* and *Saccharomyces rouxii*. Examples of *Kluyveromyces* are *Kluyveromyces*
25 *fragilis* and *Kluyveromyces lactis*. Examples of *Hansenula* are *Hansenula polymorpha*, *Hansenula anomala* and *Hansenula capsulata*. *Yarrowia lipolytica* is an example of a suitable *Yarrowia* species.

Methods for the transformation of *S. cerevisiae* are taught generally in EP 251 744, EP 258 067 and WO 90/01063, all of which are incorporated herein by reference.

- 5 Suitable promoters for *S. cerevisiae* include those associated with the *PGK1* gene, *GAL1* or *GAL10* genes, *CYC1*, *PHO5*, *TRP1*, *ADH1*, *ADH2*, the genes for glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, triose phosphate isomerase, phosphoglucose isomerase, glucokinase, α -mating factor pheromone, a-
- 10 mating factor pheromone, the *PRB1* promoter, the *GUT2* promoter, and hybrid promoters involving hybrids of parts of 5' regulatory regions with parts of 5' regulatory regions of other promoters or with upstream activation sites (e.g. the promoter of EP-A-258 067).
- 15 The transcription termination signal is preferably the 3' flanking sequence of a eukaryotic gene which contains proper signals for transcription termination and polyadenylation. Suitable 3' flanking sequences may, for example, be those of the gene naturally linked to the expression control sequence used, i.e. may correspond to the promoter. Alternatively, they
- 20 may be different in which case the termination signal of the *S. cerevisiae* *AHD1* gene is preferred.

The present invention also relates to a host cell transformed with a polynucleotide vector construct of the present invention. The host cell can

25 be either procaryotic or eukaryotic. Bacterial cells are preferred procaryotic host cells and typically are a strain of *E. coli* such as, for example, the *E. coli* strains DH5 available from Bethesda Research Laboratories Inc., Bethesda, MD, USA, and RR1 available from the

- American Type Culture Collection (ATCC) of Rockville, MD, USA (No ATCC 31343). Preferred eukaryotic host cells include yeast and mammalian cells, preferably vertebrate cells such as those from a mouse, rat, monkey or human fibroblastic cell line. Preferred eukaryotic host
- 5 cells include Chinese hamster ovary (CHO) cells available from the ATCC as CCL61, NIH Swiss mouse embryo cells NIH/3T3 available from the ATCC as CRL 1658 and monkey kidney-derived COS-1 cells available from the ATCC as CRL 1650 or WSØ cells.
- 10 Transformation of appropriate cell hosts with a nucleic acid constructs of the present invention is accomplished by well known methods that typically depend on the type of vector used. With regard to transformation of procaryotic host cells, see, for example, Cohen *et al*, *Proc. Natl. Acad. Sci. USA*, 69: 2110 (1972); and Sambrook *et al*,
- 15 *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989). Transformation of yeast cells is described in Sherman *et al*, *Methods In Yeast Genetics, A Laboratory Manual*, Cold Spring Harbor, NY (1986). The method of Beggs, *Nature*, 275: 104-109 (1978) is also useful. With regard to
- 20 vertebrate cells, reagents useful in transfecting such cells, for example calcium phosphate and DEAE-dextran or liposome formulations, are available from Stratagene Cloning Systems, or Life Technologies Inc, Gaithersburg, MD 20877, USA.
- 25 Successfully transformed cells, *i.e.* cells that contain a nucleic acid construct of the present invention, can be identified by well known techniques. For example, cells resulting from the introduction of an expression construct of the present invention can be grown to produce the

polypeptide of the invention. Cells can be harvested and lysed and their DNA content examined for the presence of the DNA using a method such as that described by Southern, *J. Mol. Biol.*, 98: 503 (1975) or Berent *et al*, *Biotech.*, 3: 208 (1985). Alternatively, the presence of the protein in
5 the supernatant can be detected using antibodies as described below.

In addition to directly assaying for the presence of recombinant nucleic acid, successful transformation can be confirmed by well known immunological methods when the recombinant nucleic acid is capable of
10 directing the expression of the protein. For example, cells successfully transformed with an expression vector produce proteins displaying appropriate antigenicity. Samples of cells suspected of being transformed are harvested and assayed for the protein using suitable antibodies.

15 Thus, in addition to the transformed host cells themselves, the present invention also contemplates a culture of those cells, preferably a monoclonal (clonally homogeneous) culture, or a culture derived from a monoclonal culture, in a nutrient medium. Preferably, the culture also contains the protein.

20

Nutrient media useful for culturing transformed host cells are well known in the art and can be obtained from several commercial sources.

A third aspect of the invention provides a vector comprising a nucleic acid
25 according to the second aspect of the invention.

A fourth aspect of the invention provides a host cell comprising a vector according to the third aspect of the invention.

Preferably, the host cell is a mammalian cell.

More preferably the host cell is NS0 or CHO.

5

A fifth aspect of the invention provides a pharmaceutical composition comprising a compound according to the first aspect of the invention and a pharmaceutically acceptable carrier.

10 The compounds and compositions of the invention are administered in any suitable way, usually parenterally, for example intravenously, intraperitoneally or, preferably (for bladder cancer), intravesically (*i.e.* into the bladder), in standard sterile, non-pyrogenic formulations of diluents and carriers, for example isotonic saline (when administered
15 intravenously).

A sixth aspect of the invention provides a compound according to the first aspect of the invention for use in medicine.

20 The compounds and compositions of the invention may be used to treat a patient with any disease involving a dysfunction of a population of cells expressing PEM, said compounds and compositions selectively targeting and destroying said population of cells within a patient. For example, said compounds and compositions may be used in the treatment of cancer, *e.g.*
25 cancer of the breast, ovaries, lung, stomach, intestines, blood *etc.* Thus, anti-tumour cell antigen antibodies can be used to deliver a cytotoxic portion with endonuclease activity to a tumour cell. Antibodies that are internalised upon contact with the target antigen are used, such that the

cytotoxic portion enters the cytosol of the tumour cell, where it can trigger cell death.

In principle, the compounds and compositions of the invention may be used to treat any mammal, including pets such as dogs and cats and agriculturally important animals such as cows, horses, sheep and pigs.

Preferably, the patient is human.

10 A seventh aspect of the invention provides the use of a compound according to first aspect of the invention in the preparation of a medicament for treating a mammal having said target cells to be destroyed.

15 Preferably, the medicament is for treating cancer, such as ovarian cancer.

A eighth aspect of the invention provides a method of treating a mammal having target cells to be destroyed, the method comprising administering a compound according to the first aspect of the invention to said mammal.

20

In a preferred embodiment of the seventh and eighth aspects of the invention, the mammal is a human.

Preferably, the target cells to be destroyed are cancer cells. More preferably, the cancer cells are epithelial cancer cells, such as ovarian, gastric, colorectal and/or pancreatic cancer cells. Most preferably, the cancer cells are ovarian cancer cells.

25

The invention will now be described in detail with reference to the following figures and examples:

Figure 1 shows the complete coding sequence of human DNase I.

5

Figure 2 shows (A) the mature DNase peptide I sequence used in the exemplary Ab-DNase and Fab-DNase constructs, and (B) a truncated DNase peptide I sequence encoded by a nucleotide sequence comprising a Kozak sequence (underlined).

10

Figure 3 shows (A) the nucleotide sequence encoding the humanised HMFG1 light chain including leader peptide, (B) the nucleotide sequence of (A) further comprising a Kozak sequence (underlined), (C) the amino acid sequence of the humanised HMFG1 light chain including leader peptide (shaded) and (D) the nucleotide sequence encoding the humanised HMFG1 heavy chain including leader peptide,

15

Figure 4 shows the linker and hinge-linker oligonucleotides used in (A) the whole antibody-DNase and (B) the Fd-DNase exemplary constructs.

20 Note, in Figure 4(A) a deletion of one or more codons between the HMFG1 hinge and the linker is represented as Δ G.

Figure 5 shows nucleotide sequences (A and B) encoding a humanised HMFG-1 Fd/DNase I fusion pAS23 comprising a leader sequence (underlined) and a linker sequence (double-underlined). Figure 5(C) shows the nucleotide sequence of (B) further comprising a Kozak sequence (underlined). Figure (D) shows the amino acid sequence of a humanised HMFG-1 Fd/DNase I fusion.

25

Figure 6 shows (A), (B) and (C) shows the nucleotide sequences of Figure 5 (A), (B) and (C), respectively, further comprising an SV40 NLS (double underlined) (pAS27). Figure (D) shows the amino acid sequence of a
5 humanised HMFG-1 Fd/DNase I fusion comprising an SV40 NLS (double underlined).

Figure 7 shows (A) the nucleotide sequence and (B) the translated amino acid sequence of an exemplary HMFG-1 heavy chain/DNase I fusion
10 pAS34 (as used in 'Ab-DNase' in Example 2), comprising a leader sequence (underlined) and a linker sequence (double-underlined).

Figure 8 shows (A) the nucleotide sequence and (B) the translated amino acid sequence of an exemplary HMFG-1 heavy chain/DNase I fusion
15 pAS35, comprising a leader sequence (underlined) and a linker sequence (double-underlined). The lower case 'g' represents a silent mutation caused by PCR amplification.

Figure 9 shows (A) the nucleotide sequence and (B) the translated amino acid sequence of an exemplary HMFG-1 heavy chain/DNase I fusion
20 pAS36, comprising a leader sequence (underlined) and a linker sequence (double-underlined). The lower case 'c' represents a silent mutation caused by PCR amplification.

25 Figure 10 shows (A) the nucleotide sequence and (B) the translated amino acid sequence of an exemplary HMFG-1 heavy chain/DNase I fusion pAS37, comprising a leader sequence (underlined), a linker sequence (double-underlined) and an NLS sequence (triple underlined).

Figure 11 shows (A) the nucleotide sequence and (B) the translated amino acid sequence of an exemplary HMFG-1 heavy chain/DNase I fusion pAS38, comprising a leader sequence (underlined), a linker sequence (double-underlined) and an NLS sequence (triple underlined). The lower case 'g' represents a silent mutation caused by PCR amplification.

Figure 12 shows (A) the nucleotide sequence and (B) the translated amino acid sequence of an exemplary HMFG-1 heavy chain/DNase I fusion pAS39, comprising a leader sequence (underlined), a linker sequence (double-underlined) and an NLS sequence (triple underlined). The lower case 'c' represents a silent mutation caused by PCR amplification.

Figure 13 shows nucleotide sequences (A and B) encoding a humanised HMFG-1 Fd/DNase I fusion pAS101 comprising a short leader sequence (underlined) and a linker sequence (double-underlined). Figure 13(C) shows the nucleotide sequence of (B) further comprising a Kozak sequence (underlined). Figure (D) shows the amino acid sequence of a humanised HMFG-1 Fd/DNase I fusion.

Figure 14 shows nucleotide sequences (A and B) encoding a humanised HMFG-1 Fd/DNase I fusion pAS102 comprising a leader sequence (underlined) and a hybrid hinge + linker sequence (double-underlined).

Figure 14(C) shows the nucleotide sequence of (B) further comprising a Kozak sequence (underlined) (construct designated pAS302 in Example 2). Figure (D) shows the amino acid sequence of a humanised HMFG-1 Fd/DNase I fusion.

Figure 15 shows nucleotide sequences (A and B) encoding a humanised HMFG-1 Fd/DNase I fusion pAS103 comprising a leader sequence (underlined) and a hybrid hinge + short linker sequence (double-underlined). Figure 15(C) shows the nucleotide sequence of (B) further comprising a Kozak sequence (underlined). Figure (D) shows the amino acid sequence of a humanised HMFG-1 Fd/DNase I fusion.

Figure 16 shows nucleotide sequences (A and B) encoding a humanised HMFG-1 Fd/DNase I fusion pAS104 comprising a leader sequence (underlined) and a hybrid hinge + mutated short linker sequence (double-underlined). Figure (C) shows the amino acid sequence of a humanised HMFG-1 Fd/DNase I fusion. Mutations (compared to pAS103) at positions 775 and 924 are shaded.

Figure 17 shows nucleotide sequences (A and B) encoding a humanised HMFG-1 Fd/DNase I fusion pAS105 comprising a leader sequence (underlined), a short linker sequence (double-underlined) and an NLS sequence (triple underlined). Figure 17(C) shows the nucleotide sequence of (B) further comprising a Kozak sequence (underlined). Figure (D) shows the amino acid sequence of a humanised HMFG-1 Fd/DNase I fusion.

Figure 18 shows nucleotide sequences (A and B) encoding a humanised HMFG-1 Fd/DNase I fusion pAS106 comprising a leader sequence (underlined), a hybrid hinge + linker sequence (double-underlined) and an NLS sequence (triple underlined). Figure 18(C) shows the nucleotide sequence of (B) further comprising a Kozak sequence (underlined). Figure (D) shows the amino acid sequence of a humanised HMFG-1

Fd/DNase I fusion.

Figure 19 shows nucleotide sequences (A and B) encoding a humanised HMFG-1 Fd/DNase I fusion pAS107 comprising a leader sequence (underlined), a hybrid hinge + short linker sequence (double-underlined) and an NLS sequence (triple underlined). Figure 19(C) shows the nucleotide sequence of (B) further comprising a Kozak sequence (underlined). Figure (D) shows the amino acid sequence of a humanised HMFG-1 Fd/DNase I fusion.

10

Figure 20 shows a schematic diagram of the pEE6 expression vector used in the exemplary constructs.

Figure 21 shows autoradiographs from immuno-precipitation experiments with metabolically labelled transient transfectants:

15

GEL A

Lane 1 shows the precipitation of supernatant from mock-transfected cells.

20

Lane 2 is from cells transfected with hHMFG-1 (construct 6) giving expected molecular weights of about 51.2 and 26.4 kDa for the heavy and light chains, respectively.

25

Lane 3 shows construct 34 antibody construct which has human DNase I fused to the C-terminus of the heavy chain gene. As expected, the size of the heavy chain gene has increased to about 80.7 kDa.

Samples from whole antibody DNase I constructs 35, 36 and 39 were run on the gel (Lanes 4 to 6) but were not sufficiently well

expressed to be visible, in this experiment.

In subsequent experiments using this method, construct 39 was detectable but weak, and constructs 35 and 36 were detectable but very weak. Constructs 37 and 38 have not been tested in this assay system.

Lanes 8 to 10 are fusion of humanised HMFG1 F(ab')₂ with human DNase I (constructs 41, 23 and 102, respectively). F(ab')₂ alone was included in this set of experiments (lane 7, construct 41) but did not express, this was included in later experiments (see gels C and D).

In addition to the light chain (about 26.4 kDa) and the Fd-DNase I fusion (about 56.6 kDa), a third major band is observed at around 40 kDa. Interestingly, this band is observed in the humanised HMFG-1 fusions but not in the antibody alone. Since an anti-F(ab')₂ antibody was used for immuno-precipitation, it is unlikely that this can be proteolysis between immunoglobulin and DNase I sequence.

It probably represents a population of polypeptide produced by premature transcriptional termination (due to DNase I sequence in the 3'-end of the fusion mRNA).

GEL B

This is the non-reducing gel counterpart to gel A, described above.

Lane 1 is the mock-transfected control cells and lanes 2 and 3 are from the cells transfected with humanised HMFG1 alone (construct 6) and the humanised HMFG-1 fused at the C-terminus to human DNase I, respectively. As before, lanes 4 to 6 are from cell supernatants from cells transfected with constructs 35, 36 and 39.

The gel shows that both the whole antibody and the antibody-DNase I fusion are assembled, with the DNase fusion giving a higher

molecular weight compared to the antibody alone.

Figure 22 shows a typical standard curve used to determine the concentration of PDTRP-binding material in the supernatants of transiently transfected L761h cells. Each point on the curve has been determined twice.

Figure 23 shows typical standard curves used to determine the concentration of bovine DNase I.

10

Figure 24 shows corrected DNase I activity in transiently expressed humanised HMFG1 whole antibody-human DNase I fusions (*i.e.* pAS34, pAS34, pAS35 and pAS6[control]).

15 Figure 25 shows the corrected DNase I activity in transiently expressed humanised HMFG1 F(ab')₂-human DNase I fusions (*i.e.* pAS101, pAS102, pAS103 and pAS41[control]).

Figure 26 shows results of the cytotoxicity assay.

20

Figure 27 shows the % of MCF7 cells killed after incubation with the exemplary constructs.

Figure 28 shows a schematic diagram of (A) Ab-DNase and (B) Fab-DNase.

25

Figure 29 shows a schematic diagram of vector pAS34K encoding Ab-DNase (*i.e.* pAS34 as shown in Figure 7b plus Kozak sequence).

Figure 30 shows a schematic diagram of vector pAS302 encoding Fab-DNase.

- 5 Figure 31 shows (A) the elution profile from Protein-L column and (B) size exclusion chromatogram for Fab-DNase.

Figure 32 shows (A) the elution profile from Protein-A column and (B) size exclusion chromatogram for Ab-DNase.

10

Figure 33 shows the SDS-PAGE stained gels for (A) Ab-DNase and (B) Fab-DNase.

- Figure 34 shows (A) standard curve for bovine DNase concentration AND
15 (B) DNase activity measurements at 3 hours and 6 hours.

Figure 35 shows (A) PEM expression on OVCAR 3 and A375 cells, as measured by ELISA using hHMFG-1 and AD-DNase antibodies, and (B) cytotoxicity measurements.

20

EXAMPLES

Example 1

5 (A) Mammalian expression of humanised HMFG1-DNase constructs

The human HMFG1 light and heavy chain (with or without engineering a fusion to human DNase I), were cloned into the pEE6 expression vector system for expression in mammalian CHO or myeloid NS0 cells (see
10 figure 20). The vector system was originally developed by Celltech Ltd (UK) and is now owned by al-Lonza (see Young & Owens, 1994, *J. Immunol. Meth.* 168:149-165). The vector consists of two human cytomegalovirus promoters (hCMV) for both the heavy and light chain genes. Each transcription unit is completed by the poly-adenylation signal
15 (pA) with an optional immunoglobulin terminator sequence (Ig term.) located between the heavy and light chain transcription units. Propagation in *E.coli* can be selected for by the presence on an ampicillin resistance gene (not shown in Fig 20). The inclusion of a glutamine synthetase gene (GS) in the vector allows the stable NS0 transfectomas to be selected by
20 growth in glutamine free media, since NS0 cells are GS⁻ and cannot otherwise grow in glutamine free media.

Exemplary humanized HMFG1-DNase I fusion constructs of the invention are detailed in figures 5 to 19.

25

(B) Immuno-precipitation of metabolically labelled transient transfectants

CHO-L761h cells (Cockett *et al.*, 1990, *Nuc. Acids Res.* 19:319-325)

were transfected, according to the modification of Gorman et al, 1985), with expression vectors containing either whole HMFG1 antibody or F(ab')₂ fragment of the antibody along with the various fusion constructs of their respective heavy chains and human DNase I. The cells were then
5 incubated with either 50 μ Ci ³⁵S methione for 72 h in methionine-free medium. Secreted product was precipitated with a rabbit anti-human F(ab')₂ antibody bound to protein A Sepharose. Bound material was eluted in either reducing or non-reducing SDS-PAGE loading buffer and run on gels. The autoradiographs (see Figure 21) above were generated
10 from those gels after drying them.

(C) Estimation of the efficiency of DNase constructs in supernatants

Introduction

15

This set of experiments was designed to standardise the amount of construct in a given DNase I activity assay and to allow us to comment on the amount of activity a particular construct possesses. Given that the antibody-DNase I fusions are so different to the F(ab')₂-DNase I fusions
20 it is best not to compare the two groups. Once we have purified the protein, we will have a better idea of the exact molecular configuration of all species. Then, and only then, will it be sensible to compare amongst groups.

25 *Determination of concentration of constructs*

The concentration of constructs in supernatants from transiently transfected L761H cells was determined in a PDTRP-binding ELISA. To

each well of a Maxisorb 96-well ELISA plate (Nunc) was added 100 μ l of carbonate buffer containing 100 ng of recombinant GST-(PDTRP)₇ fusion protein (Gendler *et al.*, 1990, *J. Mol. Biol.* 265:15286-93). After overnight binding at 4°C, the plate was washed three times in PBS-Tween
5 (*i.e.* PBS containing 0.05% Tween-20). The plate was then blocked with three 3-minute washes of PBS-Tween containing 1% BSA.

For each construct, 100 μ l of supernatant was added to a well on the plate.

In addition, hHMFG-1 of known concentration was serially diluted down
10 the plate using doubling dilutions in 100 μ l of PBS-Tween per well. The plate was incubated for a further 1 h at 30°C, then 200 ng of MC135 anti-human kappa light chain antibody (binding site) in 100 μ l of PBS-Tween was added to each well for 1 h at 30°C. After three 3-minute washes in
15 PBS-Tween, 100 μ l of anti-mouse IgG-peroxidase conjugate (Jackson 315-035-045), diluted 1:2000 in PBS-Tween, was added to each well and incubated for 1 h at 30°C. Following a final set of three 3-minute washes in PBS-Tween, 100 μ l of TMB substrate (Sigma) was added to each well of the plate and, after a colour developed, the optical density at 630 nm of the solution in each well of the plate was determined.

20

Results

(see Figure 22)

25 (D) Corrected bovine DNase I standard curves and DNase assay

DNase activity was determined using a modification of the methyl green-DNA complex degradation method (Sinicropi *et al.*, 1994, *Analyt.*

Biochem. 222:351-358). Briefly, a 1:1 solution of the assay buffer and methyl green-salmon sperm DNA complex was mixed together to give a total volume of 0.2 ml. To this, 0.1 ml of tissue culture supernatant from transiently transfected CHO-L761h cells was added and the mixture
5 incubated at 37°C. DNA cleavage by DNase results in a reduction in absorbance at 620 nm. Figure 23 shows a standard curve produced with various concentrations of bovine DNase I over a number a time point.

Figures 24 and 25 show DNase activity for the whole HMFG1 antibody-
10 and F(ab')₂ - DNase fusions, respectively.

(E) Cytotoxicity of DNase constructs

Method

15

DNase constructs were transfected into CHO L761h cells using a calcium phosphate co-precipitation method (Gorman *et al.*, 1985, In: *DNA cloning* (2nd edition), Glover A(ed.), Academic Press, NY, 163-188). Included in the experiment were negative controls, consisting of cells transfected
20 with TE buffer alone or with TE buffer and pEE6 expression vector. In addition to these controls, vectors that express hHMFG-1 (pAS6) and F(ab')₂ of hHMFG1 (both with specificity for PEM but without DNase I) were included.

25 The supernatant from these cells was harvested after 72 h of expression, followed by centrifugation to remove dead cells. MCF-7 cells were incubated for 1 h at 37°C with an aliquot of each of these supernatants. The amount of cellular lactate dehydrogenase (LDH) released from the

MCF-7 cells due to the cytotoxicity of the supernatant was determined using the CytoTox96 cytotoxic assay kit (Promega). Total lysis ('total LDH') was determined by measuring the target cell maximum LDH release using the kits lysis solution. The percentage of cells killed was then calculated as the proportion of the LDH released to the total LDH released. For each construct, the cytotoxicity assay was performed in quadruplicate, except for assay of pAS38 and 39, which were performed in triplicate. The values of LDH release for each construct were compared against either $F(ab')_2$ or whole antibody, or each other, using a one-tailed t-test in Excel.

Results

Figures 26 and 27 shows that there is negligible cell killing with either pAS6 (HMFG1 alone) or with pAS41 ($F(ab')_2$ alone). All of the hHMFG1 $F(ab')_2$ -DNase I constructs kill significantly more cells than the $F(ab')_2$ fragment alone ($p < 0.00193$) and all of the antibody-DNase I constructs kill significantly more cells than antibody alone ($p < 0.00783$), except for perhaps pAS34 ($p < 0.021$).

(F) Use of the DNase-I/huHMFG-1 Fab fusion protein in the treatment of ovarian cancer

Patients diagnosed with ovarian cancer are treated by intravenous injection of the DNaseI/huHMFG-1 Fab fusion protein. Typically, a dose of between 1 to 100 mg will be administered weekly.

Therapeutic response is measured by the normal clinical procedures that

are well known in the art, for example radio-imaging methods.

Example 2

5 (A) Mammalian expression of humanised HMFG-1 / DNase constructs

In a second series of experiments, two further humanised HMFG-1/Dnase constructs were expressed in mammalian cells. The first construct encoded a fusion protein a complete hHMFG-1 antibody fused with human
10 DNase, designated 'Ad-DNase'. The second construct encoded a fusion protein a Fab fragment of the hHMFG-1 antibody fused with human DNase, designated 'Fab-DNase'. Ad-Dnase and Fab-DNase are shown schematically in Figure 28.

15 Ad-DNase comprises an HMFG-1 light chain as shown in Figure 3(c) and an HMFG-1 heavy chain/DNase fusion as shown in Figure 7(b).

Fab-DNase comprises an HMFG-1 light chain as shown in Figure 3(c) and an HMFG-1 Fd chain/DNase fusion as shown in Figure 14(d).

20

The human HMFG1 heavy and light chain constructs were cloned into the pEE6 expression vector system for expression in mammalian CHO or myeloid NS0 cells, as described in Section (A) of Example 1. This vector consists of two human cytomegalovirus promoters (hCMV) for both the
25 heavy and light chain genes. Each transcription unit is completed by the poly-adenylation signal (pA) with an optional immunoglobulin terminator sequence (Ig term.) located between the heavy and light chain transcription units. The vectors also comprise a 5'-UT Kozak sequence

(to enhance translation of the mRNA) and an ATG initiator codon upstream of both heavy and light chains.

The vectors encoding Ad-Dnase and Fab-DNase, designated pAS34K and
5 pAS 302 respectively, are shown schematically in Figure 32.

Propagation in *E.coli* can be selected for by the presence on an ampicillin resistance gene. The inclusion of a glutamine synthetase gene (GS) in the vector allows the stable NS0 transfectomas to be selected by growth in
10 glutamine free media, since NS0 cells are GS⁻ and cannot otherwise grow in glutamine free media.

These plasmids were co-transfected with a vector containing a neomycin resistance gene into CHO cells. Stable cell lines were generated for each
15 of the constructs.

Clones were selected that expressed DNase activity and antigen (PEM)-binding activity.

20 (B) Purification of hHMFG-1/DNase constructs

The cells were routinely grown in:

	DMEM (Gibco 10938-025)	500 ml
25	Non essential amino acids (Sigma M7145)	5 ml
	Sodium pyruvate (Sigma S8636)	5 ml
	Glutamine (G7513)	5 ml
	Heat inactivated foetal calf serum	50 ml

Incubation was carried out at 37°C in 5% CO₂.

For production of the Ab-DNase fusion protein, W70 cells (CHO cells
5 transfected with pAS34K) were maintained in flats and grown to
confluency in T175 flasks. Each T175 flask was split between two
850 cm² roller bottles containing 100 ml of the aforementioned growth
media. Each roller bottle was gassed with an 95% air 5% CO₂ mix for 1
minute and then sealed. They were rolled at a rate of 0.5 rpm and were
10 gassed every other day as described earlier until the cultures were
confluent. At this stage the medium was removed and 200 ml of harvest
medium was replaced on the culture. This was the same medium but
contained 2 mM sodium butyrate (with or without 10% heat inactivated
FCS). The cells were then grown for a further 3-4 days before they were
15 harvested. The medium was collected from the cells and dead cells were
removed from the medium by centrifugation at 5000 rpm for 30 mins at
4°C. The spun medium (supernatant) was then filtered through a 0.2
micron filter unit, prior to applying to the affinity chromatography
column.

20

The Fab-DNase fusion product was then purified by affinity
chromatography using a Protein-L column (Protein L agarose, P3351 from
Sigma Co, Poole, Dorset, UK), as follows:

- 25 1. Wash 1 ml of settled protein L agarose (P3351) with at least 5
volumes of phosphate buffered saline (PBS: 10 mM phosphate
buffered saline, pH 7.4).
2. Dilute 1 ml supernatant with 9 ml PBS.

3. Mix diluted supernatant with protein-L agarose and incubate with gentle end over end mixing for 1 hour at room temperature.
4. Pack the slurry in a column and drain.
5. Wash away unbound proteins with 10-15 column volumes of PBS.
- 5 6. Elute bound protein with 5 ml elution buffer (0.1 M glycine, pH 2.0, or 0.2 M citrate buffer, pH 2.8).
7. Neutralise eluted material with Tris-base to achieve pH 7.5.

Figure 31(a) shows the elution profile of the Fab-DNase from the Protein-L column when eluted with 0.1 M glycine, pH 2.0.

Following purification, Fab-DNase was analysed by analytical size-exclusion chromatography on a Superdex-200 column.

15 Figure 31(b) shows the size-exclusion chromatogram obtained for the Fab-DNase.

The Ab-DNase fusion product was purified by affinity chromatography using a Protein-A sepharose column, as follows:

20

1. 25 ml of protein A sepharose fast flow resin (Amersham Pharmacia Biotech) in an XK26 column (Amersham Pharmacia Biotech) was equilibrated in 0.1M glycine, pH 8.8, 0.5M NaCl.
2. Approximately 2 litres of sterile-filtered supernatant from cell line W70 (CHO cell line making 34K) was passed the column overnight at a low flow rate (1-2 ml/min).
- 25 3. The column was then washed down to base-line and was re-equilibrated in 0.15M disodium hydrogen phosphate, pH 9.0 and the

bound 34K was eluted by running a gradient between this buffer (A) and a low pH buffer (B) which consisted of 0.1M citric acid, pH2.0, supplemented to 2 mM calcium chloride and 2 mM magnesium sulphate. The gradient was run over 100 ml at a flow rate of 4 ml/min and a further 50 ml of buffer B was run over the column at the completion of the gradient, also at 4 ml/min.

4. During the 100 ml gradient and the last 50 ml of buffer A fractions were collected. The peak fractions were identified and pooled and dialysed against 4 litres of 25 mM Hepes, pH7.5, 0.2 M NaCl, 1mM calcium chloride and 1mM magnesium sulphate. Dialysis was performed overnight at 4C.
5. The dialysate was concentrated on Centricon spin concentrators to a final concentration of 6-13 mg/ml. The concentration was determined by dividing by its extinction coefficient of 1.558 (calculated from the known sequence).

Figure 32(a) shows the elution profile of the Ab-DNase from the Protein-L column when eluted with a gradient of 0.15 M Na_2HPO_4 , pH 9.0 to 0.1 M citric acid, pH 2.0 containing 2mM each of CaCl_2 and MgCl_2 .

Figure 32(b) shows the size-exclusion chromatogram obtained for the Ab-DNase.

(C) Determination of concentration of fusion proteins

Prior to measuring DNase activity of the purified fusion proteins (see Section (E) below), the concentration of the proteins was determined by ELISA, as follows (see also Section (C) of Example 1).

Materials

1. 96 Well ELISA plates (Nunc F96 Maxisorp Cat No. 442404).
- 5 2. Bovine serum albumin (Sigma A-9647).
3. Coating buffer (Na₂CO₃ 1.59 g/l, NaHCO₃ 2.93 g/l, NaN₃ 0.2 g/l, pH9.6).
4. GST-MUC1-7TR antigen (1.5 mg/ml).
5. Anti-human kappa light-chain antibody GD12 (0.2 mg/ml, Binding Site, MC135).
- 10 6. Peroxidase-conjugated rabbit anti-mouse IgG (Jackson, 315-035-045).
7. TMB- substrate buffer (Sigma P-4417).
8. Tween 20 (Sigma P7949).
- 15 9. Purified humanised HMFG1 (1.4 mg/ml).

Method

Note all washes in this protocol consist of 3 x 3 min washes in PBS buffer
20 (note: all PBS buffer contained 0.05 % Tween) and the plate was incubated in a lunch box containing moist tissue paper.

1. Coat 100 ng of antigen/100 μ l coating buffer/well overnight at 4°C.
- 25 2. Wash the plate and block each well with 100 μ l of PBS containing 0.05 % Tween, and 1% BSA for 1 h at 30°C. Wash plate afterwards.
3. A standard curve of humanised HMFG1 should be prepared

down the plate using doubling dilutions. Make each dilution in 100 μ l PBS buffer and for the highest concentration in the curve use 1000 ng of antibody.

4. Incubate the plate for 2 h at 30°C, wash, and add 100 μ l PBS containing 200 ng of the anti-human Kappa light chain antibody to each well of the plate. Incubate for a further 1 h at 30°C and then wash the plate.
5. Add 100 μ l PBS containing the rabbit anti-mouse IgG-peroxidase conjugate (diluted 1:2000) to each well of the plate and incubate for 30 min at 30°C. Wash the plate and add 100 μ l TMB- substrate-buffer to each well of the plate and allow the reaction to proceed in the dark at room temperature. When the blue colour has developed, read the plate at a wavelength of 630 nm.

15

(D) SDS-PAGE

Following purification of Ab-DNase and Fab-DNase, the fusion proteins were analysed by SDS-PAGE under non-reducing and reducing conditions, as described in Section (B) of Example 1.

20

In brief, affinity-purified material was used. In the case of the Ab-DNase fusion protein, this was from a sample dialysed and concentrated (as described in the protein A protocol above). In the case of the Fab-DNase, this was unconcentrated protein directly eluted from the protein L affinity column. 15 μ l of the Fab-DNase protein-L eluate was mixed with 5 μ l of either reducing or non-reducing loading buffer whereas 2 μ l of the Ab-DNase protein A eluate (dialysed and concentrated) was mixed with 5 μ l

25

of either reducing or non-reducing buffer. Both samples were boiled for 5 minutes and were loaded onto the gel. The gels were stained with Coomassie Brilliant Blue stain. The cells were not labelled with ³⁵S-methionine (as in Example 1).

5

The SDS-PAGE autoradiograph for Ab-DNase is shown in Figure 33(a). Under reducing conditions, Ab-DNase produces a band of about 80 kDa, which corresponds to the expected size of the heavy chain-DNase fusion product (see lane 3). A further band of about 50 kDa is also observed,
10 which is approximately the same molecular weight as the hHMFG-1 heavy chain (see lane 4).

The SDS-PAGE autoradiograph for Fab-DNase is shown in Figure 33(b). Under reducing conditions, Fab-DNase produces a band of about 55-
15 60 kDa, which corresponds to the expected size of Fab-DNase (see lane 3). Under non-reducing conditions, a band of about 80-85 kDa is observed, which is the approximate molecular weight of Fab-DNase rather than F(ab')₂-DNase (see lane 4). Thus, the Fab-DNase appears to exist as a dimer of the hHMFG-1 light chains and the hHMFG-1 heavy
20 chain/human DNase fusion, not a tetrameric F(ab')₂-DNase.

(E) Measurement of DNase activity of hHMFG-1/DNase constructs

DNase activity of the two fusion proteins was determined as described in
25 Section (D) of Example 1. In brief, 0.1 ml of the purified protein was added to a 1:1 solution of assay buffer and methyl green-salmon sperm DNA complex, and the mixture incubated at 37°C. A reduction in absorbance at 620 nm is indicative of DNA activity.

A standard curve produced using bovine DNase I is shown in Figure 34(a).

- 5 Figure 34(b) shows the DNase activity of the Fab-DNase and Ab-DNase fusion proteins 3 h and 6 h after being added to the DNA, compared to a positive control of bovine DNase and a negative control of Fab only. Clearly, the DNase activity of the Fab-DNase and Ab-DNase fusion proteins is comparable to that of the bovine DNase positive control.

10

(F) Cytotoxicity of DNase activity of hHMFG-1/DNase constructs

- Cytotoxicity of the Fab-DNase and Ab-DNase fusion proteins was analysed using two tumour cell lines, the human malignant melanoma cell
15 line A375 and the human ovarian adenocarcinoma cell line OVCAR 3.

An initial cell-based ELISA was performed using hHMFG-1 antibodies to determine the level of expression of PEM (the MUC1 gene product) on these cells.

20

Cell-based PEM ELISA assay protocol

Materials and methods

25

1. Phosphate buffered saline tablets (Sigma P-4417)
2. 50% glutaraldehyde solution (BDH UN2810 Prod. 2868240)
3. sodium azide (Sigma S-8032)
4. Nunclon 96 well tissue culture plate (Nunc D167008)

5. BSA (Sigma A-9647)
6. OVCAR-3 ovarian cancer cells, A375 melanoma cancer cells both from ATCC
7. TMB substrate buffer (Sigma P-4417)
- 5 8. Tween 20 (Sigma P7949)
9. Purified humanised HMFG1 (1 mg/ml from ICRF)
10. RPMI 1640 media (Gibco 21875-034)

Protocol

- 10 1. The OVCAR-3 and A375 cells were grown in RPMI containing 20% and 10% FCS respectively at 37°C in 5% CO₂ in a 96 well tissue culture plate, seeded at 10⁶ cells/ml with 0.1 ml/well.
- 15 2. Excess media was removed and the plate was fixed with 0.05% glutaraldehyde in water for 1 hour at room temperature.
3. Excess glutaraldehyde/water solution was removed and the plates were washed three times with PBS containing 0.05% Tween 20. The plate was stored at 4°C until required in PBS with 0.02% sodium azide).
- 20 4. To use the plate, the plate was then washed with three washes of PBS containing 0.05% Tween 20, and the wells were blocked with 0.1 ml 5% BSA in PBS containing 0.05% Tween 20. The wells were blocked for 1 hour at 30°C.
- 25 5. They washed three times as described before. Serial dilutions of hHMFG1 were plated out on the wells from a maximum concentration of 2 µg/ml downward. Dilutions of constructs were also similarly plated onto the fixed cells. All dilutions were prepared in PBS containing 0.05% Tween 20.

6. The proteins were incubated with the fixed cells for 1 hour at 30°C and were again washed three times as described above.
7. Anti-human IgG-Fc peroxidase conjugate antibody (Jackson 209-035-103) was diluted to 1:2000 in PBS containing 0.05% Tween
5 20. This was incubated at 30°C for 30 minutes.
8. Once again the cells were washed as described as before. Then 0.1 ml TMB substrate was put in each well and the colour was developed at room temperature and the absorbance at 655 nm was determined.

10

For comparison, an additional ELISA using Ab-DNase was performed with the OVCAR 3 cells.

Antigen-bound hHMFG-1 and Ab-DNase was detected by a peroxidase-
15 conjugated anti-human Fc antibody.

The results of the ELISA are shown in Figure 35, indicating that the OVCAR 3 cell line expresses high levels of PEM (as measured by both hHMFG-1 and Ab-DNase) while the A375 cell line expresses low levels
20 of PEM (and hence can be used as a negative control in cytotoxicity experiments).

Cytotoxicity was measured using an LDH release assay, as described in Section (E) of Example 1. In brief, 10^5 cells per well of the A375 and
25 OVCAR 3 cell lines were plated in a 96-well plate and grown for 24 hours. Fifteen microlitres of the purified fusion proteins (containing 200 ng of Ab-DNase or 100 ng of Fab-DNase) were added to the cells and incubated for 48 hours at 37°C. A negative control group of each cell

type was treated with 200 ng of the hHMFG-1 antibody (*i.e.* not fused to DNase).

5 Following the incubation period, 50 μ l of the supernatant was removed and incubated with 50 μ l of tetrazolium-containing substrate buffer for 30 minutes at 22°C. The reaction was stopped with stop buffer (Promega) and the absorbance of the reaction mixture at 490 nm measured.

10 Both Fab-DNase and Ab-DNase fusions show cell killing of OVCAR 3 cells as compared to the negative control hHMFG-1 treated cells. In contrast, killing of A375 cells by DNase fusions is negligible, consistent with negligible binding of the fusions to these cells.

CLAIMS

1. A compound comprising a target cell-specific portion and a cytotoxic portion characterised in that:
 - (i) the target cell-specific portion comprises an humanised monoclonal antibody having specificity for polymorphic epithelial mucin (PEM), or an antigen binding fragment thereof; and
 - (ii) the cytotoxic portion has endonucleolytic activity.
2. A compound according to Claim 1 wherein the target cell-specific portion comprises an humanised HMFG-1 antibody or an antigen binding fragment thereof.
3. A compound according to Claim 2 wherein the target cell-specific portion is an humanised HMFG-1 antibody.
4. A compound according to Claim 1 or 2 wherein the target cell-specific portion comprises an antigen binding fragment of the humanised antibody selected from the group consisting of Fab-like molecules, such as Fab and F(ab')₂, Fv molecules, disulphide-linked Fv molecules, ScFv molecules and single domain antibodies (dAbs).
5. A compound according to Claim 4 wherein the target cell-specific portion comprises a Fab molecule.
6. A compound according to Claim 4 wherein the target cell-specific

portion comprises a $F(ab')_2$ molecule.

7. A compound according to Claim 1 wherein the target cell-specific portion comprises an amino acid sequence encoded by at least part of one or both of the nucleotide sequences of Figure 3(a) and (d).
8. A compound according to Claim 7 wherein the target cell-specific portion comprises an amino acid sequence encoded by the nucleotide sequence of Figure 3(a) and an amino acid sequence encoded by the nucleotide sequence of Figure 3(d).
9. A compound according to any one of Claims 1 to 8 wherein the cytotoxic portion has DNA endonucleolytic activity.
10. A compound according to Claim 9 wherein the cytotoxic portion is at least the catalytically active portion of a DNA endonuclease.
11. A compound according to Claim 10 wherein the endonuclease is a mammalian deoxyribonuclease I.
12. A compound according to Claim 11 wherein the endonuclease is a human deoxyribonuclease I.
13. A compound according to Claim 1 wherein the endonuclease is a restriction endonuclease.
14. A compound according to Claim 10 wherein the cytotoxic portion comprises the amino acid sequence shown in Figure 2(a) or (b).

15. A compound according to any one of Claims 1 to 14 wherein a nuclear localization signal is incorporated.
16. A compound according to Claim 15 wherein the nuclear localization signal comprises the sequence PKKKRKV.
17. A compound according to any one of Claims 1 to 16 wherein the target cell-specific portion and the cytotoxic portion are fused.
18. A compound according to Claim 17 wherein the target cell-specific portion and the cytotoxic portion are separated by a linker sequence.
19. A compound according to Claim 18 wherein the linker sequence is or comprises GG or GSGG.
20. A compound according to any one of Claims 1 to 19 wherein the compound comprises all or part of the amino acid sequence as shown in Figure 3(c) together with all or part of an amino acid sequence selected from the group consisting of amino acid sequences as shown in Figures 5(d), 6(d), 7(b), 8(b), 9(b), 10(b), 11(b), 12(b), 13(d), 14(d), 15(d), 16(c), 17(d), 18(d) and 19(d).
21. A compound according to Claim 20 wherein the compound comprises an amino acid sequence as shown in Figure 3(c) and an amino acid sequence as shown in Figure 7(b).
22. A compound according to Claim 20 wherein the compound comprises

an amino acid sequence as shown in Figure 3(c) and an amino acid sequence as shown in Figure 14(d).

23. A nucleic acid molecule encoding a compound as defined in any one of Claims 1 to 22.
24. A nucleic acid molecule according to Claim 23 wherein the molecule comprises all or part of the nucleotide sequence as shown in Figure 3(a or b) together with all or part of a nucleotide sequence selected from the group consisting of nucleotide sequences as shown in Figures 5(a, b and c), 6(a, b and c), 7(a), 8(a), 9(a), 10(a), 11(a), 12(a), 13(a, b and c), 14(a, b and c), 15(a, b and c), 16(a and b), 17(a, b and c), 18(a, b and c) and 19(a, b and c).
25. A nucleic acid molecule according to Claim 24 wherein the molecule comprises a nucleotide sequence as shown in Figure 3(b) and a nucleotide sequence as shown in Figure 7(a).
25. A nucleic acid molecule according to Claim 24 wherein the molecule comprises a nucleotide sequence as shown in Figure 3(b) and a nucleotide sequence as shown in Figure 14(c).
26. A nucleic acid molecule according to any one of Claims 23 to 25 wherein the molecule further comprises a Kozak consensus ribosome-binding site.
27. A vector comprising a nucleic acid molecule according to any one of Claims 23 to 26.

28. A host cell comprising a vector according to Claim 27.
29. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 22 and a pharmaceutically acceptable carrier.
30. A compound according to any one of Claims 1 to 22 for use in medicine.
31. Use of a compound according to any one of Claims 1 to 22 in the preparation of a medicament for treating a mammal having said target cells to be destroyed.
32. A method of treating a mammal having target cells to be destroyed, the method comprising administering a compound according to any one of Claims 1 to 22 to said mammal.
33. A use according to Claim 31 or a method according to Claim 32 wherein the mammal is a human.
34. A use according to Claim 31 or a method according to Claim 32 wherein the target cells to be destroyed are cancer cells.
35. A use or a method according to Claim 34 wherein the cancer cells are epithelial cancer cells.
36. A use or a method according to Claim 35 wherein the cancer cells are ovarian, gastric, colorectal and/or pancreatic cancer cells.

37. A use or a method according to Claim 36 wherein the cancer cells are ovarian cancer cells.
38. A compound substantially as described herein, preferably with reference to one or more of the accompanying figures.

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Human DNase I

LOCUS HUMDNASEI 1039 bp mRNA PRI 06-MAR-1995
 DEFINITION Human DNase I mRNA, complete cds.
 ACCESSION M55983
 VERSION M55983.1 GI:181623
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 SOURCE Human pancreas, cDNA to mRNA.
 ORGANISM Homo sapiens
 Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Mammalia;
 Eutheria; Primates; Catarrhini; Hominidae; Homo.
 REFERENCE 1 (bases 1 to 1039)
 AUTHORS Shak, S., Capon, D.J., Hellmiss, R., Marsters, S.A. and Baker, C.L.
 TITLE Recombinant human DNase I reduces the viscosity of cystic fibrosis
 sputum
 JOURNAL Proc. Natl. Acad. Sci. U.S.A. 87 (23), 9188-9192 (1990)
 MEDLINE 91067672
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//

Fig. 1

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Human DNase I construct

LOCUS MHDNASE.DN 783 bp mRNA PRI 06-MAR-1995
 DEFINITION Human DNase I mRNA, complete cds, Mature sequence modified to remove NarI site
 ACCESSION M55983
 NID g181623
 KEYWORDS DNase I.
 SOURCE Human pancreas, cDNA to mRNA.
 ORGANISM Homo sapiens
 Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata; Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
 REFERENCE 1 (bases 1 to 1039)
 AUTHORS Shak, S., Capon, D.J., Hellmiss, R., Marsters, S.A. and Baker, C.L.
 TITLE Recombinant human DNase I reduces the viscosity of cystic fibrosis sputum
 JOURNAL Proc. Natl. Acad. Sci. U.S.A. 87 (23), 9188-9192 (1990)
 MEDLINE 91067672
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Fig. 2(A)

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 KEYWORDS -
 SOURCE -

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//

Fig. 2(B)

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pAS6 – light chain

LOCUS HMFG1LC2.D 721 bp DNA 18-AUG-1998
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 ACCESSION
 KEYWORDS
 SOURCE
 ORGANISM
 REFERENCE 1 (BASES 1 TO 342)
 AUTHORS VERHOEYEN ET AL
 TITLE CONSTRUCTION OF RESHAPED HMFG1 ETC
 JOURNAL IMMUNOL. (1993):78, 364-370
 COMMENT SCANNED IN FROM JOURNAL
 FEATURES
 SITES

This is the sequence of the HMFG1 light chain gene with the
 Vnp leader sequence attached. Translate from
 residue 1. Note residue 399 is T > A in all clones leading
 to R133 silent mutation (T in Verhoeven paper)

BASE COUNT 197 a 202 c 182 g 140 t
 ORIGIN ?

```

x      LEADER SEQ
1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCGGAC
61 ATCCAGATGA CCCAGAGCCC AAGCAGCCTG AGCGCCAGCG TGGGTGACAG AGTGACCATC
121 ACCTGTAAGT CCAGTCAGAG CCTTTTATAT AGTAGCAATC AAAAGATCTA CTTGGCCTGG
181 TACCAGCAGA AGCCAGGTAA GGCTCCAAAG CTGCTGATCT ACTGGGCATC CACTAGGGAA
241 TCTGGTGTGC CAAGCAGATT CAGCGGTAGC GGTAGCGGTA CCGACTTCAC CTTACCATC
301 AGCAGCCTCC AGCCAGAGGA CATCGCCACC TACTACTGCC AGCAATATTA TAGATATCCT
361 CGGACGTTTC GCCAAGGGAC CAAGGTGGAA ATCAAACGAA CTGTGGCTGC ACCATCTGTC
421 TTCATCTTCC CGCCATCTGA TGAGCAGTTG AAATCTGGAA CTGCCTCTGT TGTGTGCCTG
481 CTGAATAACT TCTATCCAG AGAGGCCAAA GTACAGTGGA AGGTGGATAA CGCCCTCCAA
541 TCGGGTAACT CCCAGGAGAG TGTCACAGAG CAGGACAGCA AGGACAGCAC CTACAGCCTC
601 AGCAGCACCC TGACGCTGAG CAAAGCAGAC TACGAGAAAC ACAAAGTCTA CGCCTGCGAA
661 GTCACCCATC AGGCCTGAG CTCGCCCGTC ACAAAGAGCT TCAACAGGGG AGAGTGTTAG
721 A
  
```

//

Fig. 3(A)

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LOCUS      HHMFG1KLC_      730 BP SS-DNA      SYN      29-AUG-2000
DEFINITION -
ACCESSION -
KEYWORDS   -
SOURCE     -
FEATURES   Location/Qualifiers
            frag          10..730
                        /note="1 to 721 of hHMFG1light chain"
            frag          10..730
                        /note="1 to 72 of 104linker"
            frag          join(10..>63,<65..81)
                        /note="1 to 72 of 103linker [Split]"
            frag          join(10..>60,<61..>63,<65..81)
                        /note="1 to 78 of 102linker [Split]"
BASE COUNT      198 A      208 C      184 G      140 T      0 OTHER
ORIGIN         -
      1  GCGGCCACCA TGGGATGGAG CTGTATCATC CTCTTCTTGG TAGCAACAGC TACAGGTGTC
     61  CACTCCGACA TCCAGATGAC CCAGAGCCCA AGCAGCCTGA GCGCCAGCGT GGGTGACAGA
    121  GTGACCATCA CCTGTAAGTC CAGTCAGAGC CTTTATATA GTAGCAATCA AAAGATCTAC
    181  TTGGCCTGGT ACCAGCAGAA GCCAGGTAAG GCTCCAAAGC TGCTGATCTA CTGGGCATCC
    241  ACTAGGGAAT CTGGTGTGCC AAGCAGATTC AGCGGTAGCG GTAGCGGTAC CGACTTCACC
    301  TTCACCATCA GCAGCCTCCA GCCAGAGGAC ATCGCCACCT ACTACTGCCA GCAATATTAT
    361  AGATATCCTC GGACGTTCGG CCAAGGGACC AAGGTGGAAA TCAAACGAAC TGTGGCTGCA
    421  CCATCTGTCT TCATCTTCCC GCCATCTGAT GAGCAGTTGA AATCTGGAAC TGCCTCTGTT
    481  GTGTGCCTGC TGAATAACTT CTATCCCAGA GAGGCCAAAG TACAGTGGAA GGTGGATAAC
    541  GCCCTCCAAT CGGGTAAGTC CCAGGAGAGT GTCACAGAGC AGGACAGCAA GGACAGCACC
    601  TACAGCCTCA GCAGCACCTT GACGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC
    661  GCCTGCGAAG TCACCCATCA GGGCCTGAGC TCGCCCGTCA CAAAGAGCTT CAACAGGGGA
    721  GAGTGTTAGA

```

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Fig. 3(B)

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HMFG-1 light chain with Vnp Leader (shaded)

MCWSCIEELVATATGVHS
LYSSNQKIYLA WYQQKPGKAPKLLIWASTRESGVPSRFSGSGSGT
DFTFTISLQPEDATYYCQYYRYPRTFGQGTKVEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV
TEQDSKDSSTLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN
RGEC

Fig. 3(C)

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pAS6 – heavy chain

LOCUS HMMFG1HC.D 1404 bp DNA 14-AUG-1998
 DEFINITION HUMANISED HMMFG1 heavy chain
 ACCESSION HMMFG1H
 KEYWORDS
 SOURCE
 ORGANISM
 REFERENCE
 AUTHORS VERHOEYEN ET AL
 TITLE CONSTRUCTION OF RESHAPED HMMFG1 etc
 JOURNAL IMMUNOL. (1993):78, 364-370
 COMMENT VH domain SCANNED IN FROM JOURNAL
 FEATURES AA RESIDUE 235 HAS NOT BEEN CHANGED TO KABAT (I.E. V TO A)
 FEATURES Residue 963 is G > T leading to silent mutation in all clones
 SITES Note
 BASE COUNT 333 a 439 c 379 g 253 t
 ORIGIN ?

← LEADER

```

1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCAGTGCC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCAGCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGGTGC GTGGAATCA
541 GCGGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCTCT AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAATCTTGT
721 GACAAACTC ACACATGCCC ACCGTGCCCA GCACCTGAAC TCCTGGGGGG ACCGTCAGTC
781 TTCCTCTTCC CCCCAGAAC CAAGGACACC CTCATGATCT CCCGGACCCC TGAGGTCACA
841 TGCGTGGTGG TGGACGTGAG CCACGAAGAC CCTGAGGTCA AGTTCAACTG GTACGTGGAC
901 GCGGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG AGCAGTACAA CAGCACGTAC
961 CGTGTGGTCA GCCTCCTCAC CGTCTGTCAC CAGGACTGGC TGAATGGCAA GGAGTACAAG
1021 TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA AAACCATCTC CAAAGCCAAA
1081 GGGCAGCCCC GAGAACCACA GGTGTACACC CTGCCCCCAT CCCGGGATGA GCTGACCAAG
1141 AACCAGGTCA GCCTGACCTG CCTGGTCAAA GGCTTCTATC CCAGCGACAT CGCCGTGGAG
1201 TGGGAGAGCA ATGGGCAGCC GGAGAACAAC TACAAGACCA CGCCTCCCGT GCTGGACTCC
1261 GACGGCTCCT TCTTCCTCTA CAGCAAGCTC ACCGTGGACA AGAGCAGGTG GCAGCAGGGG
1321 AACGTCTTCT CATGCTCCGT GATGCATGAG GCTCTGCACA ACCACTACAC GCAGAAGAGC
1381 CTCTCCCTGT CTCCGGGTAA ATGA
  
```

Antibody DNase Fusions Made Here
(eg pAS34----39.)

End of lower hinge region of heavy chain. PAPE Amino
Acid Seq. Fab'₂ fusions were made at this point.

Those with HYBRID HINGES are altered further
up

This part GACAAACTGACACA
D K T H T

After this sequence you get the HYBRID HINGE + LINKER SEQUENCES
Then DNase I (eg Fab-DNase construct pAS302)

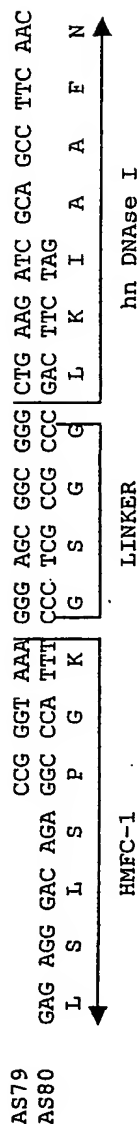
Fig. 3(D)

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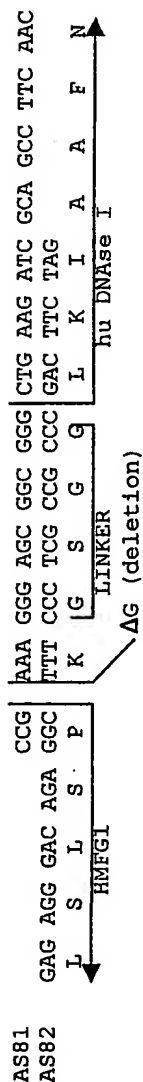
Fig. 4(A)

Oligos involved in the fusion of whole antibody-DNase

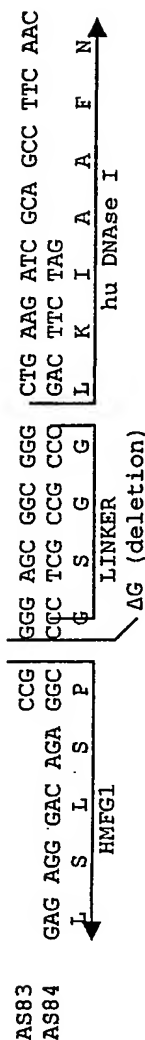
Constructs pAS34/37



Constructs pAS35/38

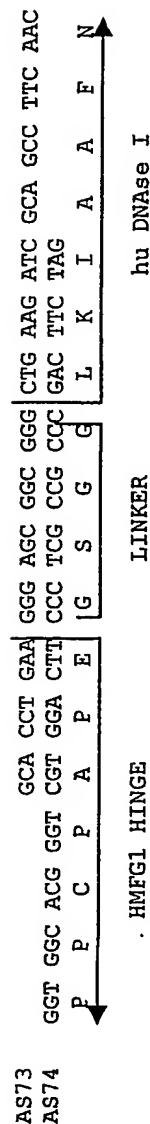


Constructs pAS36/39



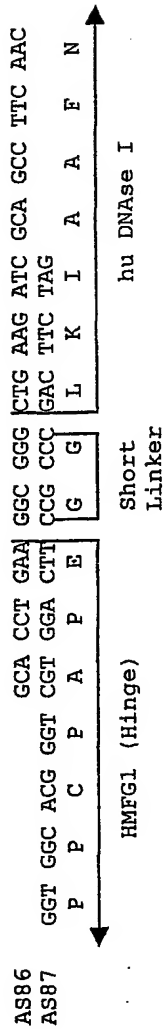
Oligos involved in the fusion of Fab'2-DNaseI

Constructs pAS23/27

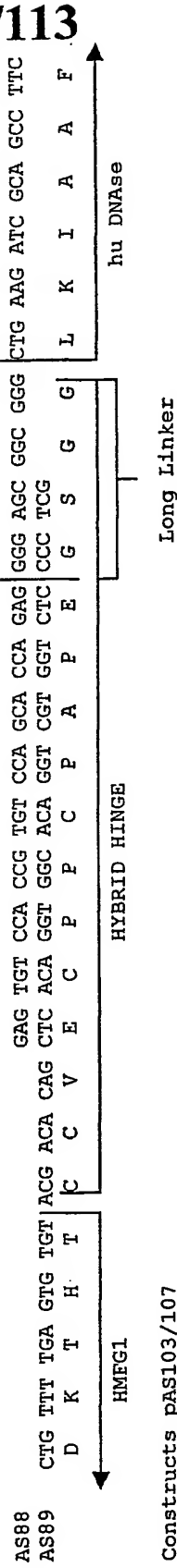


Oligos involved in the fusion of new Fab'2-DNaseI molecules (5.7.99)

Constructs pAS101/105



Constructs pAS102/106



Constructs pAS103/107

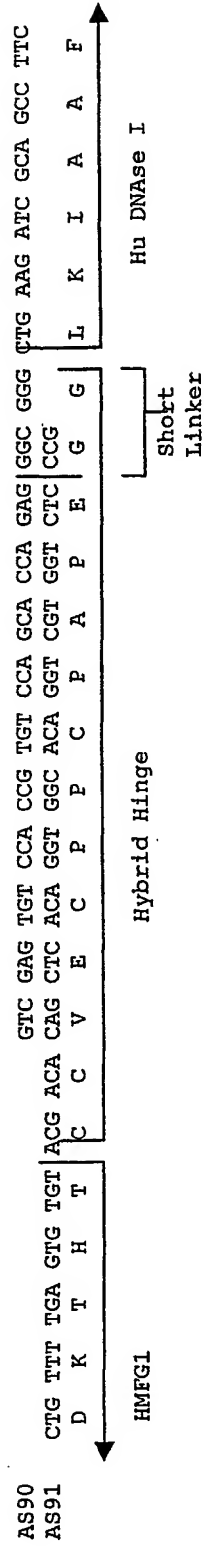


Fig. 4(B)

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pAS23

LOCUS PAS23.DNA 1554 bp mRNA PRI 06-MAR-1995
 DEFINITION Humanised HMFG1 Fab'2 fused to human DNase I (construct 1)
 ACCESSION
 NID
 KEYWORDS DNase I.
 SOURCE DNase I sequence is from assembled oligos (thus modified c/f
 MHDNASE1.dna)
 ORGANISM Homo sapiens
 Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
 Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
 AUTHORS Shak, S., Capon, D.J., Hellmiss, R., Marsters, S.A. and Baker, C.L.
 TITLE Recombinant human DNase I reduces the viscosity of cystic
 fibrosis
 sputum
 JOURNAL Proc. Natl. Acad. Sci. U.S.A. 87 (23), 9188-9192 (1990)
 MEDLINE 91067672
 BASE COUNT 344 a 468 c 434 g 308 t
 ORIGIN

```

1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCAAGTGC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGGTGC GTGGAAC TCA
541 GGCGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAACTC ACACATGCCC ACCGTGCCCA GCACCTGAAG GGAGCGGCGG GCTGAAGATC
781 GCAGCCTTCA ACATCCAGAC ATTTGGGGAG ACCAAGATGT CCAATGCCAC CCTCGTCAGC
841 TACATTGTGC AGATCCTGAG CCGCTACGAC ATCGCCCTGG TCCAGGAGGT CAGAGACAGC
901 CACCTGACTG CCGTGGGGAA GCTGCTGGAC AACCTCAATC AGGACGCACC AGACACCTAT
961 CACTACGTGG TCAGTGAGCC ACTGGGACGG AACAGCTATA AGGAGCGCTA CCTGTTCTGTG
1021 TACAGGCTG ACCAGGTGTC TGCGGTGGAC AGCTACTACT ACGATGATGG CTGCGAGCCC
1081 TGCGGGAACG ACACCTTCAA CCGAGAGCCA GCCATTGTCA GGTTCCTTCT CCGGTTTACA
1141 GAGGTCAGGG AGTTTGCCAT TGTTCCTCTG CATGCGGCCC CGGGGGACGC AGTAGCCGAG
1201 ATCGACGCTC TCTATGACGT CTACCTGGAT GTCCAAGAGA AATGGGGCTT GGAGGACGTC
1261 ATGTTGATGG GCGACTTCAA TGCGGGCTGC AGCTATGTGA GACCCTCCCA GTGGTCATCC
1321 ATCCGCTGTG GGACAAGCCC CACCTTCCAG TGGCTGATCC CCGACAGCGC TGACACCACA
1381 GCTACACCCA CGCACTGTGC CTATGACAGG ATCGTGGTTG CAGGGATGCT GCTCCGAGGG
1441 GCCGTGTTC CCGACTCGGC TCTTCCCTTT AACTTCCAGG CTGCCTATGG CCTGAGTGAC
1501 CAACTGGCCC AAGCCATCAG TGACCACTAT CCAGTGGAGG TGATGCTGAA GTGA

```

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Fig. 5(A)

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LOCUS FDDNASE23_ 1554 BP SS-DNA SYN 25-AUG-2000
 DEFINITION -
 ACCESSION -
 KEYWORDS -
 SOURCE -
 FEATURES Location/Qualifiers
 frag join(1..>720,<787..1554)
 /note="1 to 1554 of 23.dna [Split]"
 frag 721..786
 /note="1 to 66 of 23/27linker"
 frag join(721..>735,<736..786)
 /note="1 to 78 of 102linker [Split]"
 BASE COUNT 344 A 466 C 435 G 309 T 0 OTHER
 ORIGIN -

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1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCACTGCC TACTGGATAG ACTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAACCTCA
541 GCGGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCTTC AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAAATC ACACATGTCC ACCGTGTCCA GCACCAAGAG GGAGCGGCGG GCTGAAGATC
781 GCAGCCTTCA ACATCCAGAC ATTTGGGGAG ACCAAGATGT CCAATGCCAC CCTCGTCAGC
841 TACATTGTGC AGATCCTGAG CCGCTACGAC ATCGCCCTGG TCCAGGAGGT CAGAGACAGC
901 CACCTGACTG CCGTGGGGAA GCTGCTGGAC AACCTCAATC AGGACGCACC AGACACCTAT
961 CACTACGTGG TCAGTGAGCC ACTGGGACGG AACAGCTATA AGGAGCGCTA CCTGTTCGTG
1021 TACAGGCCTG ACCAGGTGTC TGCGGTGGAC AGCTACTACT ACGATGATGG CTGCGAGCCC
1081 TGCGGGAACG ACACCTTCAA CCGAGAGCCA GCCATTGTCA GGTCTTCTC CCGGTTTACA
1141 GAGGTCAGGG AGTTTGCCAT TGTTCCCCTG CATGCGGCCC CGGGGGACGC AGTAGCCGAG
1201 ATCGACGCTC TCTATGACGT CTACCTGGAT GTCCAAGAGA AATGGGGCTT GGAGGACGTC
1261 ATGTTGATGG GCGACTTCAA TGCGGGCTGC AGCTATGTGA GACCCTCCCA GTGGTCATCC
1321 ATCCGCCTGT GGACAAGCCC CACCTTCCAG TGGCTGATCC CCGACAGCGC TGACACCACA
1381 GCTACACCCA CGCACTGTGC CTATGACAGG ATCGTGGTTG CAGGGATGCT GCTCCGAGGG
1441 GCCGTTGTTC CCGACTCGGC TCTTCCCTTT AACTTCCAGG CTGCCTATGG CCTGAGTGAC
1501 CAACTGGCCC AAGCCATCAG TGACCACTAT CCAGTGGAGG TGATGCTGAA GTGA

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Fig. 5(B)

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LOCUS FDDNASE23K 1563 BP SS-DNA SYN 29-AUG-2000
 DEFINITION -
 ACCESSION -
 KEYWORDS -
 SOURCE -
 FEATURES
 Location/Qualifiers
 frag 10..1563
 /note="1 to 1554 of FdDNase23correct"
 frag join(10..>729,<796..1563)
 /note="1 to 1554 of 23.dna [Split]"
 frag 730..795
 /note="1 to 66 of 23/27linker"
 frag join(730..>744,<745..795)
 /note="1 to 78 of 102linker [Split]"
 BASE COUNT 345 A 472 C 437 G 309 T 0 OTHER
 ORIGIN -
 1 GCCGCCACCA TGGGATGGAG CTGTATCATC CTCTTCTTGG TAGCAACAGC TACAGGTGTC
 61 CACTCCCAGG TGCAGCTGGT GCAGTCTGGG GCAGAGGTGA AAAAGCCTGG GGCCTCAGTG
 121 AAGGTGTCCT GCAAGGCTTC TGGCTACACC TTCAGTGCCT ACTGGATAGA GTGGGTGCGC
 181 CAGGCTCCAG GAAAGGGCCT CGAGTGGGTC GGAGAGATTT TACCTGGAAG TAATAATTCT
 241 AGATACAATG AGAAGTTCAA GGGCCGAGTG ACAGTCACTA GAGACACATC CACAAACACA
 301 GCCTACATGG AGCTCAGCAG CCTGAGGTCT GAGGACACAG CCGTCTATTA CTGTGCAAGA
 361 TCCTACGACT TTGCCTGGTT TGCTTACTGG GGCCAAGGGA CTCTGGTCAC AGTCTCCTCA
 421 GCCTCCACCA AGGGCCCATC GGTCTTCCCC CTGGCACCCCT CCTCCAAGAG CACCTCTGGG
 481 GGCACAGCGG CCCTGGGCTG CCTGGTCAAG GACTACTTCC CCGAACCCTG GACGGTGTCTG
 541 TGGAACTCAG GCGCCCTGAC CAGCGGCGTG CACACCTTCC CGGCTGTCTT ACAGTCCTCA
 601 GGA CTCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAGCTTGGG CACCCAGACC
 661 TACATCTGCA ACGTGAATCA CAAGCCCAGC AACACCAAGG TGGACAAGAA AGTTGAGCCC
 721 AAATCTTGTG ACAAACCTCA CACATGTCCA CCGTGTCCAG CACCAGAGGG GAGCGGCGGG
 781 CTGAAGATCG CAGCCTTCAA CATCCAGACA TTTGGGGAGA CCAAGATGTC CAATGCCACC
 841 CTCGTACGCT ACATTGTGCA GATCCTGAGC CGCTACGACA TCGCCCTGGT CCAGGAGGTC
 901 AGAGACAGCC ACCTGACTGC CGTGGGGAAG CTGCTGGACA ACCTCAATCA GGACGCACCA
 961 GACACCTATC ACTACGTGGT CAGTGAGCCA CTGGGACGGA ACAGCTATAA GGAGCGCTAC
 1021 CTGTTCTGTG ACAGGCCTGA CCAGGTGTCT GCGGTGGACA GCTACTACTA CGATGATGGC
 1081 TGCGAGCCCT GCGGGAACGA CACCTTCAAC CGAGAGCCAG CCATTGTCAG GTTCTTCTCC
 1141 CGGTTACAG AGGTACAGGA GTTTGCCATT GTTCCCCTGC ATGCGGCCCC GGGGACGCA
 1201 GTAGCCGAGA TCGACGCTCT CTATGACGTC TACCTGGATG TCCAAGAGAA ATGGGGCTTG
 1261 GAGGACGTCA TGTGATGGG CCACTTCAAT GCGGGCTGCA GCTATGTGAG ACCCTCCCAG
 1321 TGGTCATCCA TCCGCCTGTG GACAAGCCCC ACCTTCCAGT GGCTGATCCC CGACAGCGCT
 1381 GACACCACAG CTACACCCAC GCACTGTGCC TATGACAGGA TCGTGGTTGC AGGGATGCTG
 1441 CTCCGAGGGG CCGTTGTTCC CGACTCGGCT CTTCCTTTA ACTTCCAGGC TGCCATATGGC
 1501 CTGAGTGACC AACTGGCCCA AGCCATCAGT GACCACTATC CAGTGGAGGT GATGCTGAAG
 1561 TGA

//

Fig. 5(C)

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      9      18      27      36      45      54
5'  ATG GGA TGG AGC TGT ATC ATC CTC TTC TTG GTA GCA ACA GCT ACA GGT GTC CAC
    ---
    M  G  W  S  C  I  I  L  F  L  V  A  T  A  T  G  V  H

      63      72      81      90      99      108
TCC CAG GTG CAG CTG GTG CAG TCT GGG GCA GAG GTG AAA AAG CCT GGG GCC TCA
    ---
    S  Q  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  A  S

      117      126      135      144      153      162
GTG AAG GTG TCC TGC AAG GCT TCT GGC TAC ACC TTC AGT GCC TAC TGG ATA GAG
    ---
    V  K  V  S  C  K  A  S  G  Y  T  F  S  A  Y  W  I  E

      171      180      189      198      207      216
TGG GTG CGC CAG GCT CCA GGA AAG GGC CTC GAG TGG GTC GGA GAG ATT TTA CCT
    ---
    W  V  R  Q  A  P  G  K  G  L  E  W  V  G  E  I  L  P

      225      234      243      252      261      270
GGA AGT AAT AAT TCT AGA TAC AAT GAG AAG TTC AAG GGC CGA GTG ACA GTC ACT
    ---
    G  S  N  N  S  R  Y  N  E  K  F  K  G  R  V  T  V  T

      279      288      297      306      315      324
AGA GAC ACA TCC ACA AAC ACA GCC TAC ATG GAG CTC AGC AGC CTG AGG TCT GAG
    ---
    R  D  T  S  T  N  T  A  Y  M  E  L  S  S  L  R  S  E

      333      342      351      360      369      378
GAC ACA GCC GTC TAT TAC TGT GCA AGA TCC TAC GAC TTT GCC TGG TTT GCT TAC
    ---
    D  T  A  V  Y  Y  C  A  R  S  Y  D  F  A  W  F  A  Y

      387      396      405      414      423      432
TGG GGC CAA GGG ACT CTG GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG
    ---
    W  G  Q  G  T  L  V  T  V  S  S  A  S  T  K  G  P  S

      441      450      459      468      477      486
GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC CTG
    ---
    V  F  P  L  A  P  S  S  K  S  T  S  G  G  T  A  A  L

      495      504      513      522      531      540
GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA
    ---
    G  C  L  V  K  D  Y  F  P  E  P  V  T  V  S  W  N  S

      549      558      567      576      585      594
GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA
    ---
    G  A  L  T  S  G  V  H  T  F  P  A  V  L  Q  S  S  G

```

Fig. 5(D)
(Sheet 1 of 3)

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603	612	621	630	639	648
CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG					
L Y S L S S V V T V P S S S L G T Q					
657	666	675	684	693	702
ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA					
T Y I C N V N H K P S N T K V D K K					
711	720	729	738	747	756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG TGC CCA GCA CCT					
V E P K S C D K T H T C P P C P A P					
765	774	783	792	801	810
GAA GGG AGC GGC GGG CTG AAG ATC GCA GCC TTC AAC ATC CAG ACA TTT GGG GAG					
E G S G G L K I A A F N I Q T F G E					
819	828	837	846	855	864
ACC AAG ATG TCC AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG ATC CTG AGC CGC					
T K M S N A T L V S Y I V Q I L S R					
873	882	891	900	909	918
TAC GAC ATC GCC CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG ACT GCC GTG GGG					
Y D I A L V Q E V R D S H L T A V G					
927	936	945	954	963	972
AAG CTG CTG GAC AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT CAC TAC GTG GTC					
K L L D N L N Q D A P D T Y H Y V V					
981	990	999	1008	1017	1026
AGT GAG CCA CTG GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG TTC GTG TAC AGG					
S E P L G R N S Y K E R Y L F V Y R					
1035	1044	1053	1062	1071	1080
CCT GAC CAG GTG TCT GCG GTG GAC AGC TAC TAC TAC GAT GAT GGC TGC GAG CCC					
P D Q V S A V D S Y Y Y D D G C E P					
1089	1098	1107	1116	1125	1134
TGC GGG AAC GAC ACC TTC AAC CGA GAG CCA GCC ATT GTC AGG TTC TTC TCC CGG					
C G N D T F N R E P A I V R F F S R					
1143	1152	1161	1170	1179	1188
TTC ACA GAG GTC AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG GCC CCG GGG GAC					
F T E V R E F A I V P L H A A P G D					
1197	1206	1215	1224	1233	1242

Fig. 5(D)
(Sheet 2 of 3)

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GCA GTA GCC GAG ATC GAC GCT CTC TAT GAC GTC TAC CTG GAT GTC CAA GAG AAA
-----
A V A E I D A L Y D V Y L D V Q E K

      1251      1260      1269      1278      1287      1296
TGG GGC TTG GAG GAC GTC ATG TTG ATG GGC GAC TTC AAT GCG GGC TGC AGC TAT
-----
W G L E D V M L M G D F N A G C S Y

      1305      1314      1323      1332      1341      1350
GTG AGA CCC TCC CAG TGG TCA TCC ATC CGC CTG TGG ACA AGC CCC ACC TTC CAG
-----
V R P S Q W S S I R L W T S P T F Q

      1359      1368      1377      1386      1395      1404
TGG CTG ATC CCC GAC AGC GCT GAC ACC ACA GCT ACA CCC ACG CAC TGT GCC TAT
-----
W L I P D S A D T T A T P T H C A Y

      1413      1422      1431      1440      1449      1458
GAC AGG ATC GTG GTT GCA GGG ATG CTG CTC CGA GGG GCC GTT GTT CCC GAC TCG
-----
D R I V V A G M L L R G A V V P D S

      1467      1476      1485      1494      1503      1512
GCT CTT CCC TTT AAC TTC CAG GCT GCC TAT GGC CTG AGT GAC CAA CTG GCC CAA
-----
A L P F N F Q A A Y G L S D Q L A Q

      1521      1530      1539      1548
GCC ATC AGT GAC CAC TAT CCA GTG GAG GTG ATG CTG AAG TGA 3'
-----
A I S D H Y P V E V M L K *

```

Fig. 5(D)
(Sheet 3 of 3)

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pAS27

LOCUS PAS27.DNA 1584 bp mRNA PRI 06-MAR-1995
 DEFINITION Humanised HMFG1 Fab'2 fused to human DNase I with SV40
 NLS(construct 1)
 ACCESSION
 NID
 KEYWORDS DNase I.
 SOURCE DNase I sequence is from assembled oligos (thus modified c/f
 MHDNASE1.dna)
 ORGANISM Homo sapiens
 Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
 Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
 AUTHORS Shak, S., Capon, D.J., Hellmiss, R., Marsters, S.A. and Baker, C.L.
 TITLE Recombinant human DNase I reduces the viscosity of cystic fibrosis
 sputum
 JOURNAL Proc. Natl. Acad. Sci. U.S.A. 87 (23), 9188-9192 (1990)
 MEDLINE 91067672
 BASE COUNT 354 a 474 c 446 g 310 t
 ORIGIN

```

1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCAGTGCC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAACCTCA
541 GGCGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCTC AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAACTC ACACATGCCC ACCGTGCCCA GCACCTGAAG GGAGCGGCGG GCTGAAGATC
781 GCAGCCTTCA ACATCCAGAC ATTTGGGGAG ACCAAGATGT CCAATGCCAC CCTCGTCAGC
841 TACATTGTGC AGATCCTGAG CCGCTACGAC ATCGCCCTGG TCCAGGAGGT CAGAGACAGC
901 CACCTGACTG CCGTGGGGAA GCTGCTGGAC AACCTCAATC AGGACGCACC AGACACCTAT
961 CACTACGTGG TCAGTGAGCC ACTGGGACGG AACAGCTATA AGGAGCGCTA CCTGTTCGTG
1021 TACAGGCCTG ACCAGGTGTC TGCGGTGGAC AGCTACTACT ACGATGATGG CTGCGAGCCC
1081 TGCGGGAACG ACACCTTCAA CCGAGAGCCA GCCATTGTCA GGTTCCTTCTC CCGGTTTACA
1141 GAGGTCAGGG AGTTTGCCAT TGTTCCCTTG CATGCGGCCC CGGGGGACGC AGTAGCCGAG
1201 ATCGACGCTC TCTATGACGT CTACCTGGAT GTCCAAGAGA AATGGGGCTT GGAGGACGTC
1261 ATGTTGATGG GCGACTTCAA TGCGGGCTGC AGCTATGTGA GACCTCCCA GTGGTCATCC
1321 ATCCGCTGT GGACAAGCCC CACCTTCCAG TGGCTGATCC CCGACAGCGC TGACACCACA
1381 GCTACACCCA CGCACTGTGC CTATGACAGG ATCGTGGTTG CAGGGATGCT GCTCCGAGGG
1441 GCCGTTGTTT CCGACTCGGC TCTTCCCTTT AACTTCCAGG CTGCCTATGG CCTGAGTGAC
1501 CAACTGCCCC AAGCCATCAG TGACCACTAT CCAGTGGAGG TGATGCTGAA GGGGGGCGGA
1561 CCCAAAAAGA AGCGCAAGGT TTGA

```

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Fig. 6(A)

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LOCUS FDDNASE27_ 1584 BP SS-DNA SYN 25-AUG-2000
 DEFINITION -
 ACCESSION -
 KEYWORDS -
 SOURCE -
 FEATURES Location/Qualifiers
 frag join(1..>720,<787..1584)
 /note="1 to 1584 of 27.dna [Split]"
 frag 721..786
 /note="1 to 66 of 23/27linker"
 frag join(721..>735,<736..786)
 /note="1 to 78 of 102linker [Split]"
 BASE COUNT 354 A 472 C 447 G 311 T 0 OTHER
 ORIGIN -
 1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
 61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
 121 TGCAAGGCTT CTGGCTACAC CTTAGTGCC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
 181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
 241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
 301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
 361 TTTGCCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
 421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
 481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAACCTCA
 541 GCGGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCTC AGGACTCTAC
 601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
 661 AACGTGAATC ACAAGCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
 721 GACAAACTC ACACATGTCC ACCGTGTCCA GCACCAAGAG GGAGCGGCGG GCTGAAGATC
 781 GCAGCCTTCA ACATCCAGAC ATTTGGGGAG ACCAAGATGT CCAATGCCAC CCTCGTCAGC
 841 TACATTGTGC AGATCCTGAG CCGCTACGAC ATCGCCCTGG TCCAGGAGGT CAGAGACAGC
 901 CACCTGACTG CCGTGGGGAA GCTGCTGGAC AACCTCAATC AGGACGCACC AGACACCTAT
 961 CACTACGTGG TCAGTGAGCC ACTGGGACGG AACAGCTATA AGGAGCGCTA CCTGTTCGTG
 1021 TACAGGCCTG ACCAGGTGTC TCGGGTGGAC AGCTACTACT ACGATGATGG CTGCGAGCCC
 1081 TGCGGGAAACG ACACCTTCAA CCGAGAGCCA GCCATTGTCA GGTTCCTCTC CCGGTTTACA
 1141 GAGGTCAGGG AGTTTGCCAT TGTTCCTCTG CATGCGGCCC CGGGGGACGC AGTAGCCGAG
 1201 ATCGACGCTC TCTATGACGT CTACCTGGAT GTCCAAGAGA AATGGGGCTT GGAGGACGTC
 1261 ATGTTGATGG GCGACTTCAA TGCGGGCTGC AGCTATGTGA GACCCCTCCA GTGGTCATCC
 1321 ATCCGCCTGT GGACAAGCCC CACCTTCCAG TGGCTGATCC CCGACAGCGC TGACACCACA
 1381 GCTACACCCA CGCACTGTGC CTATGACAGG ATCGTGTTG CAGGGATGCT GCTCCGAGGG
 1441 GCCGTTGTTT CCGACTCGGC TCTTCCCTTT AACTTCCAGG CTGCCATATG CCTGAGTGAC
 1501 CAACTGGCCC AAGCCATCAG TGACCACTAT CCAGTGAGG TGATGCTGAA GGGGGGCGGA
 1561 CCCAAAAAGA AGCGCAAGGT TTGA

//

Fig. 6(B)

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LOCUS FDDNASE27K 1593 BP SS-DNA SYN 29-AUG-2000

DEFINITION -

ACCESSION -

KEYWORDS -

SOURCE -

FEATURES

Location/Qualifiers

frag 10..1593

/note="1 to 1584 of FdDNase27correct"

frag join(10..>729,<796..1593)

/note="1 to 1584 of 27.dna [Split]"

frag 730..795

/note="1 to 66 of 23/27linker"

frag join(730..>744,<745..795)

/note="1 to 78 of 102linker [Split]"

BASE COUNT 355 A 478 C 449 G 311 T 0 OTHER

ORIGIN -

1 GCCGCCACCA TGGGATGGAG CTGTATCATC CTCTTCTTGG TAGCAACAGC TACAGGTGTC

61 CACTCCCAGG TGCAGCTGGT GCAGTCTGGG GCAGAGGTGA AAAAGCCTGG GGCCCTCAGTG

121 AAGGTGTCCT GCAAGGCTTC TGGCTACACC TTCAGTGCCT ACTGGATAGA GTGGGTGCGC

181 CAGGCTCCAG GAAAGGGCCT CGAGTGGGTC GGAGAGATTT TACCTGGAAG TAATAATTCT

241 AGATACAATG AGAAGTTCAA GGGCCGAGTG ACAGTCACTA GAGACACATC CACAAACACA

301 GCCTACATGG AGCTCAGCAG CCTGAGGTCT GAGGACACAG CCGTCTATTA CTGTGCAAGA

361 TCCTACGACT TTGCCTGGTT TGCTTACTGG GGCCAAGGGA CTCTGGTCAC AGTCTCCTCA

421 GCCTCCACCA AGGGCCCATC GGTCTTCCCC CTGGCACCCT CCTCCAAGAG CACCTCTGGG

481 GGCACAGCGG CCCTGGGCTG CCTGGTCAAG GACTACTTCC CCGAACCAGG GACGGTGTCTG

541 TGGAACTCAG GCGCCCTGAC CAGCGGCGTG CACACCTTCC CGGCTGTCTT ACAGTCCCTCA

601 GGA CTCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAGCTTGGG CACCCAGACC

661 TACATCTGCA ACGTGAATCA CAAGCCCAGC AACACCAAGG TGGACAAGAA AGTTGAGCCC

721 AAATCTTGTG ACAA AACTCA CACATGTCCA CCGTGTCCAG CACCAGAGGG GAGCGGCGGG

781 CTGAAGATCG CAGCCTTCAA CATCCAGACA TTTGGGGAGA CCAAGATGTC CAATGCCACC

841 CTCGTCAGCT ACATTGTGCA GATCCTGAGC CGCTACGACA TCGCCCTGGT CCAGGAGGTC

901 AGAGACAGCC ACCTGACTGC CGTGGGGAAG CTGCTGGACA ACCTCAATCA GGACGCACCA

961 GACACCTATC ACTACGTGGT CAGTGAGCCA CTGGGACGGA ACAGCTATAA GGAGCGCTAC

1021 CTGTTTCGTGT ACAGGCCTGA CCAGGTGTCT GCGGTGGACA GCTACTACTA CGATGATGGC

1081 TGCGAGCCCT GCGGGAACGA CACCTTCAAC CGAGAGCCAG CCATTGTGAG GTTCTTCTCC

1141 CGGTTACAG AGGTCAGGGA GTTTGCCATT GTTCCCTTGC ATGCGGCCCC GGGGGACGCA

1201 GTAGCCGAGA TCGACGCTCT CTATGACGTC TACCTGGATG TCCAAGAGAA ATGGGGCTTG

1261 GAGGACGTCA TGTTGATGGG CGACTTCAAT GCGGGCTGCA GCTATGTGAG ACCCTCCCAG

1321 TGGTCATCCA TCCGCCTGTG GACAAGCCCC ACCTTCCAGT GGCTGATCCC CGACAGCGCT

1381 GACACCACAG CTACACCCAC GCACTGTGCC TATGACAGGA TCGTGGTTGC AGGGATGCTG

1441 CTCGAGGGG CCGTTGTTCC CGACTCGGCT CTTCCCTTTA ACTTCCAGGC TGCCTATGGC

1501 CTGAGTGACC AACTGGCCA AGCCATCAGT GACCACTATC CAGTGGAGGT GATGCTGAAG

1561 GGGGGCGGAC CCAAAAAGAA GCGCAAGGTT TGA

//

Fig. 6(C)

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          9      18      27      36      45      54
5' ATG GGA TGG AGC TGT ATC ATC CTC TTC TTG GTA GCA ACA GCT ACA GGT GTC CAC
   -----
   M  G  W  S  C  I  I  L  F  L  V  A  T  A  T  G  V  H

          63      72      81      90      99      108
TCC CAG GTG CAG CTG GTG CAG TCT GGG GCA GAG GTG AAA AAG CCT GGG GCC TCA
   -----
   S  Q  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  A  S

          117      126      135      144      153      162
GTG AAG GTG TCC TGC AAG GCT TCT GGC TAC ACC TTC AGT GCC TAC TGG ATA GAG
   -----
   V  K  V  S  C  K  A  S  G  Y  T  F  S  A  Y  W  I  E

          171      180      189      198      207      216
TGG GTG CGC CAG GCT CCA GGA AAG GGC CTC GAG TGG GTC GGA GAG ATT TTA CCT
   -----
   W  V  R  Q  A  P  G  K  G  L  E  W  V  G  E  I  L  P

          225      234      243      252      261      270
GGA AGT AAT AAT TCT AGA TAC AAT GAG AAG TTC AAG GGC CGA GTG ACA GTC ACT
   -----
   G  S  N  N  S  R  Y  N  E  K  F  K  G  R  V  T  V  T

          279      288      297      306      315      324
AGA GAC ACA TCC ACA AAC ACA GCC TAC ATG GAG CTC AGC AGC CTG AGG TCT GAG
   -----
   R  D  T  S  T  N  T  A  Y  M  E  L  S  S  L  R  S  E

          333      342      351      360      369      378
GAC ACA GCC GTC TAT TAC TGT GCA AGA TCC TAC GAC TTT GCC TGG TTT GCT TAC
   -----
   D  T  A  V  Y  Y  C  A  R  S  Y  D  F  A  W  F  A  Y

          387      396      405      414      423      432
TGG GGC CAA GGG ACT CTG GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG
   -----
   W  G  Q  G  T  L  V  T  V  S  S  A  S  T  K  G  P  S

          441      450      459      468      477      486
GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC CTG
   -----
   V  F  P  L  A  P  S  S  K  S  T  S  G  G  T  A  A  L

          495      504      513      522      531      540
GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA
   -----
   G  C  L  V  K  D  Y  F  P  E  P  V  T  V  S  W  N  S

          549      558      567      576      585      594
GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA
   -----
   G  A  L  T  S  G  V  H  T  F  P  A  V  L  Q  S  S  G

```

Fig. 6(D)
(Sheet 1 of 3)

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603	612	621	630	639	648
CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG					
L Y S L S S V V T V P S S S L G T Q					
657	666	675	684	693	702
ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA					
T Y I C N V N H K P S N T K V D K K					
711	720	729	738	747	756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG TGC CCA GCA CCT					
V E P K S C D K T H T C P P C P A P					
765	774	783	792	801	810
GAA GGG AGC GGC GGG CTG AAG ATC GCA GCC TTC AAC ATC CAG ACA TTT GGG GAG					
E G S G G L K I A A F N I Q T F G E					
819	828	837	846	855	864
ACC AAG ATG TCC AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG ATC CTG AGC CGC					
T K M S N A T L V S Y I V Q I L S R					
873	882	891	900	909	918
TAC GAC ATC GCC CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG ACT GCC GTG GGG					
Y D I A L V Q E V R D S H L T A V G					
927	936	945	954	963	972
AAG CTG CTG GAC AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT CAC TAC GTG GTC					
K L L D N L N Q D A P D T Y H Y V V					
981	990	999	1008	1017	1026
AGT GAG CCA CTG GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG TTC GTG TAC AGG					
S E P L G R N S Y K E R Y L F V Y R					
1035	1044	1053	1062	1071	1080
CCT GAC CAG GTG TCT GCG GTG GAC AGC TAC TAC TAC GAT GAT GGC TGC GAG CCC					
P D Q V S A V D S Y Y Y D D G C E P					
1089	1098	1107	1116	1125	1134
TGC GGG AAC GAC ACC TTC AAC CGA GAG CCA GCC ATT GTC AGG TTC TTC TCC CGG					
C G N D T F N R E P A I V R F F S R					
1143	1152	1161	1170	1179	1188
TTC ACA GAG GTC AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG GCC CCG GGG GAC					
F T E V R E F A I V P L H A A P G D					
1197	1206	1215	1224	1233	1242

Fig. 6(D)
(Sheet 2 of 3)

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```

GCA GTA GCC GAG ATC GAC GCT CTC TAT GAC GTC TAC CTG GAT GTC CAA GAG AAA
-----
A  V  A  E  I  D  A  L  Y  D  V  Y  L  D  V  Q  E  K

      1251      1260      1269      1278      1287      1296
TGG GGC TTG GAG GAC GTC ATG TTG ATG GGC GAC TTC AAT GCG GGC TGC AGC TAT
-----
W  G  L  E  D  V  M  L  M  G  D  F  N  A  G  C  S  Y

      1305      1314      1323      1332      1341      1350
GTG AGA CCC TCC CAG TGG TCA TCC ATC CGC CTG TGG ACA AGC CCC ACC TTC CAG
-----
V  R  P  S  Q  W  S  S  I  R  L  W  T  S  P  T  F  Q

      1359      1368      1377      1386      1395      1404
TGG CTG ATC CCC GAC AGC GCT GAC ACC ACA GCT ACA CCC ACG CAC TGT GCC TAT
-----
W  L  I  P  D  S  A  D  T  T  A  T  P  T  H  C  A  Y

      1413      1422      1431      1440      1449      1458
GAC AGG ATC GTG GTT GCA GGG ATG CTG CTC CGA GGG GCC GTT GTT CCC GAC TCG
-----
D  R  I  V  V  A  G  M  L  L  R  G  A  V  V  P  D  S

      1467      1476      1485      1494      1503      1512
GCT CTT CCC TTT AAC TTC CAG GCT GCC TAT GGC CTG AGT GAC CAA CTG GCC CAA
-----
A  L  P  F  N  F  Q  A  A  Y  G  L  S  D  Q  L  A  Q

      1521      1530      1539      1548      1557      1566
GCC ATC AGT GAC CAC TAT CCA GTG GAG GTG ATG CTG AAG GGG GGC GGA CCC AAA
-----
A  I  S  D  H  Y  P  V  E  V  M  L  K  G  G  G  P  K

      1575      1584
AAG AAG CGC AAG GTT TGA 3'
-----
K  K  R  K  V *

```

Fig. 6D
(Sheet 3 of 3)

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pAS34

LOCUS PAS34.DNA 2196 bp 2196 bp 2196 bp DNA 14-AUG-1998
 DEFINITION HUMANISED HMFG1 heavy chain fused to human DNase construct 34
 DEFINITION Clone 16.4.2 (same as hcdnasel.dna template file)
 REFERENCE
 AUTHORS VERHOEYEN ET AL
 TITLE CONSTRUCTION OF RESHAPED HMFG1 etc
 JOURNAL IMMUNOL. (1993):78, 364-370
 COMMENT Human DNase sequence is modified as a result of oligo assembly (mhdnase.dna)
 COMMENT The fusion was made using overlapping oligos AS79 and AS80
 FEATURES AA RESIDUE 235 HAS NOT BEEN CHANGED TO KABAT (I.E. V TO A)
 FEATURES Residue 963 is G > T leading to silent mutation in all clones
 SITES Note
 BASE COUNT 501 a 677 c 607 g 411 t
 ORIGIN ?

```

1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCAAGTGC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTIONTC CCCGAACCGG TGACGGTGTC GTGGAACCTCA
541 GGGGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCTCT AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAACTC ACACATGCCC ACCGTGCCCA GCACCTGAAC TCCTGGGGGG ACCGTCAGTC
781 TTCCTCTTCC CCCCAAAACC CAAGGACACC CTCATGATCT CCCGGACCCC TGAGGTCACA
841 TGCGTGGTGG TGGACGTGAG CCACGAAGAC CCTGAGGTCA AGTTCAACTG GTACGTGGAC
901 GGGCTGGAGG TGCATAATGC CAAGACAAG CCGCGGGAGG AGCAGTACAA CAGCAGCTAC
961 CGTGTGGTCA GCGTCTCTAC CGTCTCTCAC CAGGACTGGC TGAATGGCAA GGAGTACAA
1021 TGCAAGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA AAACCATCTC CAAAGCCAAA
1081 GGGCAGCCCC GAGAACCACA GGTGTACACC CTGCCCCCAT CCCGGGATGA GCTGACCAAG
1141 AACCAGGTCA GCCTGACCTG CCTGGTCAA GGCTTCTATC CCAGCGACAT CGCCGTGGAG
1201 TGGGAGAGCA ATGGGCAGCC GGAGAACAAC TACAAGACCA CGCCTCCCGT GCTGGACTCC
1261 GACGGCTCCT TCTTCTCTA CAGCAAGCTC ACCGTGGACA AGAGCAGGTG GCAGCAGGGG
1321 AACGTCTTCT CATGCTCCGT GATGCATGAG GCTCTGCACA ACCACTACAC GCAGAAGAGC
1381 CTCTCCCTGT CTCCGGGTAA AGGGAGCGGC GGGCTGAAGA TCGCAGCCTT CAACATCCAG
1441 ACATTTGGGG AGACCAAGAT GTCCAATGCC ACCCTCGTCA GCTACATTGT GCAGATCCTG
1501 AGCCGCTACG ACATCGCCCT GGTCCAGGAG GTCAGAGACA GCCACCTGAC TGCCGTGGGG
1561 AAGCTGCTGG ACAACCTCAA TCAGGACGCA CCAGACACCT ATCACTACGT GGTCACTGAG
1621 CCACTGGGAC GGAACAGCTA TAAGGAGCGT TACCTGTTCT TGTACAGGCC TGACCAAGGTG
1681 TCTGCGGTGG ACAGCTACTA CTACGATGAT GGCTGCGAGC CCTGCGGGAA CGACACCTTC
1741 AACCGAGAGC CAGCCATTGT CAGGTTCTTC TCCCGGTTCA CAGAGGTGAG GGAGTTTGCC
1801 ATTGTTCCCC TGCATGCGGC CCCGGGGGAC GCAGTAGCCG AGATCGACGC TCTCTATGAC
1861 GTCTACCTGG ATGTCCAAGA GAAATGGGGC TTGGAGGACG TCATGTTGAT GGGCGACTTC
1921 AATGCGGGCT GCAGCTATGT GAGACCCTCC CAGTGGTCAT CCATCCGCCT GTGGACAAGC
1981 CCCACCTTCC AGTGCTGAT CCCCACAGC GCTGACACCA CAGCTACACC CACGCACTGT
2041 GCCTATGACA GGATCGTGGT TGCAGGGATG CTGCTCCGAG GGGCCGTTGT TCCCGACTCG
2101 GCTCTTCCCT TTAAGTTCCA GGCTGCCTAT GGCCTGAGTG ACCAACTGGC CCAAGCCATC
2161 AGTGACCACT ATCCAGTGGA GGTGATGCTG AAGTGA

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Fig. 7(A)

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```

          9      18      27      36      45      54
5'  ATG GGA TGG AGC TGT ATC ATC CTC TTC TTG GTA GCA ACA GCT ACA GGT GTC CAC
-----
      H   G   W   S   C   I   I   L   F   L   V   A   T   A   T   G   V   H

          63      72      81      90      99      108
TCC CAG GTG CAG CTG GTG CAG TCT GGG GCA GAG GTG AAA AAG CCT GGG GCC TCA
-----
S   Q   V   Q   L   V   Q   S   G   A   E   V   K   K   P   G   A   S

          117      126      135      144      153      162
GTG AAG GTG TCC TGC AAG GCT TCT GGC TAC ACC TTC AGT GCC TAC TGG ATA GAG
-----
      V   K   V   S   C   K   A   S   G   Y   T   F   S   A   Y   W   I   E

          171      180      189      198      207      216
TGG GTG CGC CAG GCT CCA GGA AAG GGC CTC GAG TGG GTC GGA GAG ATT TTA CCT
-----
      W   V   R   Q   A   P   G   K   G   L   E   W   V   G   E   I   L   P

          225      234      243      252      261      270
GGA AGT AAT AAT TCT AGA TAC AAT GAG AAG TTC AAG GGC CGA GTG ACA GTC ACT
-----
      G   S   N   N   S   R   Y   N   E   K   F   K   G   R   V   T   V   T

          279      288      297      306      315      324
AGA GAC ACA TCC ACA AAC ACA GCC TAC ATG GAG CTC AGC AGC CTG AGG TCT GAG
-----
      R   D   T   S   T   N   T   A   Y   M   E   L   S   S   L   R   S   E

          333      342      351      360      369      378
GAC ACA GCC GTC TAT TAC TGT GCA AGA TCC TAC GAC TTT GCC TGG TTT GCT TAC
-----
      D   T   A   V   Y   Y   C   A   R   S   Y   D   F   A   W   F   A   Y

          387      396      405      414      423      432
TGG GGC CAA GGG ACT CTG GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG
-----
      W   G   Q   G   T   L   V   T   V   S   S   A   S   T   K   G   P   S

          441      450      459      468      477      486
GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC CTG
-----
      V   F   P   L   A   P   S   S   K   S   T   S   G   G   T   A   A   L

          495      504      513      522      531      540
GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA
-----
      G   C   L   V   K   D   Y   F   P   E   P   V   T   V   S   W   N   S

          549      558      567      576      585      594
GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA
-----
      G   A   L   T   S   G   V   H   T   F   P   A   V   L   Q   S   S   G

          603      612      621      630      639      648
CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG
-----
      L   Y   S   L   S   S   V   V   T   V   P   S   S   S   L   G   T   Q

          657      666      675      684      693      702

```

Fig. 7(B)
(Sheet 1 of 4)

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```

ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA
---
T Y I C N V N H K P S N T K V D K K

711 720 729 738 747 756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG TGC CCA GCA CCT
---
V E P K S C D K T H T C P P C P A P

765 774 783 792 801 810
GAA CTC CTG GGG GGA CCG TCA GTC TTC CTC TTC CCC CCA AAA CCC AAG GAC ACC
---
E L L G G P S V F L F P P K P K D T

819 828 837 846 855 864
CTC ATG ATC TCC CGG ACC CCT GAG GTC ACA TGC GTG GTG GTG GAC GTG AGC CAC
---
L M I S R T P E V T C V V V D V S H

873 882 891 900 909 918
GAA GAC CCT GAG GTC AAG TTC AAC TGG TAC GTG GAC GGC GTG GAG GTG CAT AAT
---
E D P E V K F N W Y V D G V E V H N

927 936 945 954 963 972
GCC AAG ACA AAG CCG CGG GAG GAG CAG TAC AAC AGC ACG TAC CGT GTG GTC AGC
---
A K T K P R E E Q Y N S T Y R V V S

981 990 999 1008 1017 1026
GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAT GGC AAG GAG TAC AAG TGC AAG
---
V L T V L H Q D W L N G K E Y K C K

1035 1044 1053 1062 1071 1080
GTC TCC AAC AAA GCC CTC CCA GCC CCC ATC GAG AAA ACC ATC TCC AAA GCC AAA
---
V S N K A L P A P I E K T I S K A K

1089 1098 1107 1116 1125 1134
GGG CAG CCC CGA GAA CCA CAG GTG TAC ACC CTG CCC CCA TCC CGG GAT GAG CTG
---
G Q P R E P Q V Y T L P P S R D E L

1143 1152 1161 1170 1179 1188
ACC AAG AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAT CCC AGC GAC
---
T K N Q V S L T C L V K G F Y P S D

1197 1206 1215 1224 1233 1242
ATC GCC GTG GAG TGG GAG AGC AAT GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG
---
I A V E W E S N G Q P E N N Y K T T

1251 1260 1269 1278 1287 1296
CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC AAG CTC ACC GTG
---
P P V L D S D G S F F L Y S K L T V

1305 1314 1323 1332 1341 1350
GAC AAG AGC AGG TGG CAG CAG GGG AAC GTC TTC TCA TGC TCC GTG ATG CAT GAG
---
D K S R W Q Q G N V F S C S V M H E

```

Fig. 7(B)
(Sheet 2 of 4)

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1359	1368	1377	1386	1395	1404
GCT CTG CAC AAC CAC TAC ACG CAG AAG AGC CTC TCC CTG TCT CCG GGT AAA GGG					
A L H N H Y T Q K S L S L S P G K <u>G</u>					
1413	1422	1431	1440	1449	1458
AGC GGC GGG CTG AAG ATC GCA GCC TTC AAC ATC CAG ACA TTT GGG GAG ACC AAG					
<u>S G G</u> L K I A A F N I Q T F G E T K					
1467	1476	1485	1494	1503	1512
ATG TCC AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG ATC CTG AGC CGC TAC GAC					
M S N A T L V S Y I V Q I L S R Y D					
1521	1530	1539	1548	1557	1566
ATC GCC CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG ACT GCC GTG GGG AAG CTG					
I A L V Q E V R D S H L T A V G K L					
1575	1584	1593	1602	1611	1620
CTG GAC AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT CAC TAC GTG GTC AGT GAG					
L D N L N Q D A P D T Y H Y V V S E					
1629	1638	1647	1656	1665	1674
CCA CTG GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG TTC GTG TAC AGG CCT GAC					
P L G R N S Y K E R Y L F V Y R P D					
1683	1692	1701	1710	1719	1728
CAG GTG TCT GCG GTG GAC AGC TAC TAC TAC GAT GAT GGC TGC GAG CCC TGC GGG					
Q V S A V D S Y Y Y D D G C E P C G					
1737	1746	1755	1764	1773	1782
AAC GAC ACC TTC AAC CGA GAG CCA GCC ATT GTC AGG TTC TTC TCC CGG TTC ACA					
N D T F N R E P A I V R F F S R F T					
1791	1800	1809	1818	1827	1836
GAG GTC AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG GCC CCG GGG GAC GCA GTA					
E V R E F A I V P L H A A P G D A V					
1845	1854	1863	1872	1881	1890
GCC GAG ATC GAC GCT CTC TAT GAC GTC TAC CTG GAT GTC CAA GAG AAA TGG GGC					
A E I D A L Y D V Y L D V Q E K W G					
1899	1908	1917	1926	1935	1944
TTG GAG GAC GTC ATG TTG ATG GGC GAC TTC AAT GCG GGC TGC AGC TAT GTG AGA					
L E D V M L M G D F N A G C S Y V R					
1953	1962	1971	1980	1989	1998
CCC TCC CAG TGG TCA TCC ATC CGC CTG TGG ACA AGC CCC ACC TTC CAG TGG CTG					
P S Q W S S I R L W T S P T F Q W L					
2007	2016	2025	2034	2043	2052
ATC CCC GAC AGC GCT GAC ACC ACA GCT ACA CCC ACG CAC TGT GCC TAT GAC AGG					
I P D S A D T T A T P T H C A Y D R					

Fig. 7(B)
(Sheet 3 of 4)

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2061	2070	2079	2088	2097	2106
ATC GTG GTT GCA GGG ATG CTG CTC CGA GGG GCC GTT GTT CCC GAC TCG GCT CTT					

I V V A G M L L R G A V V P D S A L					
2115	2124	2133	2142	2151	2160
CCC TTT AAC TTC CAG GCT GCC TAT GGC CTG AGT GAC CAA CTG GCC CAA GCC ATC					

P F N F Q A A Y G L S D Q L A Q A I					
2169	2178	2187	2196		
AGT GAC CAC TAT CCA GTG GAG GTG ATG CTG AAG TGA 3'					

S D H Y P V E V M L K *					

Fig. 7(B)
(Sheet 4 of 4)

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pAS35

LOCUS PAS35.DNA 2193 bp 2193 bp DNA 14-AUG-1998
 DEFINITION HUMANISED HMFG1 heavy chain fused to human DNase construct 35
 DEFINITION Clone 17.12.1 with silent K to K mutation (1398 A > G)
 REFERENCE
 AUTHORS VERHOEYEN ET AL
 TITLE CONSTRUCTION OF RESHAPED HMFG1 etc
 JOURNAL IMMUNOL. (1993):78, 364-370
 COMMENT Human DNase sequence is modified as a result of oligo assembly (mhdnase.dna)
 COMMENT The fusion was made using overlapping oligos AS81 and AS82
 FEATURES AA RESIDUE 235 HAS NOT BEEN CHANGED TO KABAT (I.E. V TO A)
 FEATURES Residue 963 is G > T leading to silent mutation in all clones
 FEATURES In 17.12.1 residue 1398 is A > G (silent K to K mutation)
 SITES Note
 BASE COUNT 500 a 677 c 606 g 410 t
 ORIGIN ?

```

1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCAAGTGC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAAGTCA
541 GCGGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAACTC ACACATGCCC ACCGTGCCCA GCACCTGAAC TCCTGGGGGG ACCGTCAGTC
781 TTCCTCTTCC CCCCAAAACC CAAGGACACC CTCATGATCT CCCGGACCCC TGAGGTCACA
841 TCGTGGTGG TGGACGTGAG CCACGAAGAC OCTGAGGTCA AGTTCACTG GTACGTGGAC
901 GCGGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG AGCAGTACAA CAGCACGTAC
961 CGTGTGGTCA GCGTCTCAC CGTCTGCAC CAGGACTGGC TGAATGGCAA GGAGTACAAG
1021 TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA AAACCATCTC CAAAGCCAAA
1081 GGGCAGCCCC GAGAACCACA GGTGTACACC CTGCCCCCAT CCCGGGATGA GCTGACCAAG
1141 AACCAGGTCA GCCTGACCTG CCTGGTCAAA GGCTTCTATC CCAGCGACAT CGCCGTGGAG
1201 TGGGAGAGCA ATGGGCAGCC GGAGAACAAC TACAAGACCA CGCCTCCCGT GCTGGACTCC
1261 GACGGTCTCT TCTTCTCTA CAGCAAGCTC ACCGTGGACA AGAGCAGGTG GCAGCAGGGG
1321 AACGTCTTCT CATGCTCCGT GATGCATGAG GCTCTGCACA ACCACTACAC GCAGAAGAGC
1381 CTCTCCCTGT CTCCGAAGGG GAGCGGCGGG CTGAAGATCG CAGCCTTCAA CATCCAGACA
1441 TTTGGGGAGA CCAAGATGTC CAATGCCACC CTCGTACAGT ACATTGTGCA GATCCTGAGC
1501 CGCTACGACA TCGCCTGGT CCAGGAGGTC AGAGACAGCC ACCTGACTGC CGTGGGGAAG
1561 CTGCTGGACA ACCTCAATCA GGACGCACCA GACACCTATC ACTACGTGGT CAGTGAGCCA
1621 CTGGGACGGA ACAGCTATAA GGAGCGCTAC CTGTTCTGTT ACAGGCCTGA CCAGGTGTCT
1681 GCGGTGGACA GCTACTACTA CGATGATGGC TGCGAGCCCT GCGGGAACGA CACCTTCAAC
1741 CGAGAGCCAG CCATTGTGAG GTTCTTCTCC CGGTTACAG AGGTCAGGGA GTTTGCCATT
1801 GTTCCCTGTC ATGCGGCCCC GGGGACGCA GTAGCCGAGA TCGACGCTCT CTATGACGTC
1861 TACCTGGATG TCCAAGAGAA ATGGGGCTTG GAGGACGTCA TGTGATGGG CGACTTCAAT
1921 GCGGGCTGCA GCTATGTGAG ACCCTCCCAG TGGTCATCCA TCCGCTGTG GACAAGCCCC
1981 ACCTTCCAGT GGCTGATCCC CGACAGCGCT GACACCACAG CTACACCCAC GCACTGTGCC
2041 TATGACAGGA TCGTGGTTGC AGGGATGCTG CTCCGAGGGG CCGTTGTTCC CGACTCGGCT
2101 CTTCCCTTTA ACTTCCAGGC TGCCTATGGC CTGAGTGACC AACTGGCCCA AGCCATCAGT
2161 GACCACTATC CAGTGGAGGT GATGCTGAAG TGA

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Fig. 8(A)

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9 18 27 36 45 54
 5' ATG GGA TGG AGC TGT ATC ATC CTC TTC TTG GTA GCA ACA GCT ACA GGT GTC CAC

 M G W S C I I L F L V A T A T G V H

 63 72 81 90 99 108
 TCC CAG GTG CAG CTG GTG CAG TCT GGG GCA GAG GTG AAA AAG CCT GGG GCC TCA

 S Q V Q L V Q S G A E V K K P G A S

 117 126 135 144 153 162
 GTG AAG GTG TCC TGC AAG GCT TCT GGC TAC ACC TTC AGT GCC TAC TGG ATA GAG

 V K V S C K A S G Y T F S A Y W I E

 171 180 189 198 207 216
 TGG GTG CGC CAG GCT CCA GGA AAG GGC CTC GAG TGG GTC GGA GAG ATT TTA CCT

 W V R Q A P G K G L E W V G E I L P

 225 234 243 252 261 270
 GGA AGT AAT AAT TCT AGA TAC AAT GAG AAG TTC AAG GGC CGA GTG ACA GTC ACT

 G S N N S R Y N E K F K G R V T V T

 279 288 297 306 315 324
 AGA GAC ACA TCC ACA AAC ACA GCC TAC ATG GAG CTC AGC AGC CTG AGG TCT GAG

 R D T S T N T A Y M E L S S L R S E

 333 342 351 360 369 378
 GAC ACA GCC GTC TAT TAC TGT GCA AGA TCC TAC GAC TTT GCC TGG TTT GCT TAC

 D T A V Y Y C A R S Y D F A W F A Y

 387 396 405 414 423 432
 TGG GGC CAA GGG ACT CTG GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG

 W G Q G T L V T V S S A S T K G P S

 441 450 459 468 477 486
 GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC CTG

 V F P L A P S S K S T S G G T A A L

 495 504 513 522 531 540
 GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA

 G C L V K D Y F P E P V T V S W N S

 549 558 567 576 585 594
 GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA

 G A L T S G V H T F P A V L Q S S G

 603 612 621 630 639 648
 CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG

 L Y S L S S V V T V P S S S L G T Q

 657 666 675 684 693 702

Fig. 8(B)
(Sheet 1 of 4)

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ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA
---
T   Y   I   C   N   V   N   H   K   P   S   N   T   K   V   D   K   K

      711      720      729      738      747      756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG TGC CCA GCA CCT
---
V   E   P   K   S   C   D   K   T   H   T   C   P   P   C   P   A   P

      765      774      783      792      801      810
GAA CTC CTG GGG GGA CCG TCA GTC TTC CTC TTC CCC CCA AAA CCC AAG GAC ACC
---
E   L   L   G   G   P   S   V   F   L   F   P   P   K   P   K   D   T

      819      828      837      846      855      864
CTC ATG ATC TCC CGG ACC CCT GAG GTC ACA TGC GTG GTG GTG GAC GTG AGC CAC
---
L   M   I   S   R   T   P   E   V   T   C   V   V   V   D   V   S   H

      873      882      891      900      909      918
GAA GAC CCT GAG GTC AAG TTC AAC TGG TAC GTG GAC GGC GTG GAG GTG CAT AAT
---
E   D   P   E   V   K   F   N   W   Y   V   D   G   V   E   V   H   N

      927      936      945      954      963      972
GCC AAG ACA AAG CCG CGG GAG GAG CAG TAC AAC AGC ACG TAC CGT GTG GTC AGC
---
A   K   T   K   P   R   E   E   Q   Y   N   S   T   Y   R   V   V   S

      981      990      999      1008      1017      1026
GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAT GGC AAG GAG TAC AAG TGC AAG
---
V   L   T   V   L   H   Q   D   W   L   N   G   K   E   Y   K   C   K

      1035      1044      1053      1062      1071      1080
GTC TCC AAC AAA GCC CTC CCA GCC CCC ATC GAG AAA ACC ATC TCC AAA GCC AAA
---
V   S   N   K   A   L   P   A   P   I   E   K   T   I   S   K   A   K

      1089      1098      1107      1116      1125      1134
GGG CAG CCC CGA GAA CCA CAG GTG TAC ACC CTG CCC CCA TCC CGG GAT GAG CTG
---
G   Q   P   R   E   P   Q   V   Y   T   L   P   P   S   R   D   E   L

      1143      1152      1161      1170      1179      1188
ACC AAG AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAT CCC AGC GAC
---
T   K   N   Q   V   S   L   T   C   L   V   K   G   F   Y   P   S   D

      1197      1206      1215      1224      1233      1242
ATC GCC GTG GAG TGG GAG AGC AAT GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG
---
I   A   V   E   W   E   S   N   G   Q   P   E   N   N   Y   K   T   T

      1251      1260      1269      1278      1287      1296
CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC AAG CTC ACC GTG
---
P   P   V   L   D   S   D   G   S   F   F   L   Y   S   K   L   T   V

      1305      1314      1323      1332      1341      1350
GAC AAG AGC AGG TGG CAG CAG GGG AAC GTC TTC TCA TGC TCC GTG ATG CAT GAG
---
D   K   S   R   W   Q   Q   G   N   V   F   S   C   S   V   M   H   E

```

Fig. 8(B)
(Sheet 2 of 4)

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1359	1368	1377	1386	1395	1404
GCT CTG CAC AAC CAC TAC ACG CAG AAG AGC CTC TCC CTG TCT CCG AAG GGG AGC					
A L H N H Y T Q K S L S L S P K <u>G S</u>					
1413	1422	1431	1440	1449	1458
GGC GGG CTG AAG ATC GCA GCC TTC AAC ATC CAG ACA TTT GGG GAG ACC AAG ATG					
<u>G G</u> L K I A A F N I Q T F G E T K M					
1467	1476	1485	1494	1503	1512
TCC AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG ATC CTG AGC CGC TAC GAC ATC					
S N A T L V S Y I V Q I L S R Y D I					
1521	1530	1539	1548	1557	1566
GCC CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG ACT GCC GTG GGG AAG CTG CTG					
A L V Q E V R D S H L T A V G K L L					
1575	1584	1593	1602	1611	1620
GAC AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT CAC TAC GTG GTC AGT GAG CCA					
D N L N Q D A P D T Y H Y V V S E P					
1629	1638	1647	1656	1665	1674
CTG GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG TTC GTG TAC AGG CCT GAC CAG					
L G R N S Y K E R Y L F V Y R P D Q					
1683	1692	1701	1710	1719	1728
GTG TCT GCG GTG GAC AGC TAC TAC TAC GAT GAT GGC TGC GAG CCC TGC GGG AAC					
V S A V D S Y Y Y D D G C E P C G N					
1737	1746	1755	1764	1773	1782
GAC ACC TTC AAC CGA GAG CCA GCC ATT GTC AGG TTC TTC TCC CCG TTC ACA GAG					
D T F N R E P A I V R F F S R F T E					
1791	1800	1809	1818	1827	1836
GTG AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG GCC CCG GGG GAC GCA GTA GCC					
V R E F A I V P L H A A P G D A V A					
1845	1854	1863	1872	1881	1890
GAG ATC GAC GCT CTC TAT GAC GTC TAC CTG GAT GTC CAA GAG AAA TGG GGC TTG					
E I D A L Y D V Y L D V Q E K W G L					
1899	1908	1917	1926	1935	1944
GAG GAC GTC ATG TTG ATG GGC GAC TTC AAT GCG GGC TGC AGC TAT GTG AGA CCC					
E D V M L M G D F N A G C S Y V R P					
1953	1962	1971	1980	1989	1998
TCC CAG TGG TCA TCC ATC CGC CTG TGG ACA AGC CCC ACC TTC CAG TGG CTG ATC					
S Q W S S I R L W T S P T F Q W L I					
2007	2016	2025	2034	2043	2052
CCC GAC AGC GCT GAC ACC ACA GCT ACA CCC ACG CAC TGT GCC TAT GAC AGG ATC					
P D S A D T T A T P T H C A Y D R I					

Fig. 8(B)
(Sheet 3 of 4)

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2061	2070	2079	2088	2097	2106
GTG GTT GCA GGG	ATG CTG CTC	CGA GGG GCC	GTT GTT CCC	GAC TCG GCT	CTT CCC

V V A G	M L L	R G A	V V P	D S A	L P
2115	2124	2133	2142	2151	2160
TTT AAC TTC CAG	GCT GCC TAT	GGC CTG AGT	GAC CAA CTG	GCC CAA GCC	ATC AGT

F N F Q	A A Y	G L S	D Q L	A Q A	I S
2169	2178	2187			
GAC CAC TAT CCA	GTG GAG GTG	ATG CTG AAG	TGA 3'		

D H Y P	V E V	M L K	*		

Fig. 8(B)
(Sheet 4 of 4)

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pAS36

LOCUS PAS36.DNA 2190 bp 2190 bp DNA 14-AUG-1998

DEFINITION HUMANISED HMFG1 heavy chain fused to human DNase - construct 36

DEFINITION Clone 18.24.1 with residue 1392 T > C

REFERENCE

AUTHORS VERHOEYEN ET AL

TITLE CONSTRUCTION OF RESHAPED HMFG1 etc

JOURNAL IMMUNOL. (1993):78, 364-370

COMMENT Human DNase sequence is modified as a result of oligo assembly (mhdnase.dna)

COMMENT The fusion was made using overlapping oligos AS83 and AS84

FEATURES AA RESIDUE 235 HAS NOT BEEN CHANGED TO KABAT (I.E. V TO A)

FEATURES Residue 963 is G > T leading to silent mutation in all clones

FEATURES Residue 1392 T > C silent S to S mutation

SITES Note

BASE COUNT 498 a 678 c 605 g 409 t

ORIGIN ?

```

1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCACTGCC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTG GTGGAACCTCA
541 GGCGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAAATC ACACATGCCC ACCGTGCCCA GCACCTGAAC TCCTGGGGGG ACCGTCAGTC
781 TTCCTCTTCC CCCCCAAACC CAAGGACACC CTCATGATCT CCGGGACCCC TGAGGTCACA
841 TGCGTGGTGG TGGACGTGAG CCACGAAGAC CCTGAGGTCA AGTTCAACTG GTACGTGGAC
901 GGCGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG AGCAGTACAA CAGCAGTAC
961 CGTGTGGTCA GCGTCCTCAC CGTCTGCAC CAGGACTGGC TGAATGGCAA GGAGTACAAG
1021 TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA AAACCATCTC CAAAGCCAAA
1081 GGGCAGCCCC GAGAACCACA GGTGTACACC CTGCCCCCAT CCGGGATGA GCTGACCAAG
1141 AACCAGGTCA GCCTGACCTG CCTGGTCAAA GGCTTCTATC CCAGCGACAT CGCCGTGGAG
1201 TGGGAGAGCA ATGGGAGGCC GGAGAACAAC TACAAGACCA CGCCTCCCGT GCTGGACTCC
1261 GACGGCTCCT TCTTCTCTA CAGCAAGCTC ACCGTGGACA AGAGCAGGTG GCAGCAGGGG
1321 AACGTCTTCT CATGCTCCGT GATGCATGAG GCTCTGCACA ACCACTACAC GCAGAAGAGC
1381 CTCTCCCTGT CcCCGGGGAG CCGCGGGCTG AAGATCGCAG CCTTCAACAT CCAGACATTT
1441 GGGGAGACCA AGATGTCCAA TGCCACCCTC GTCAGCTACA TTGTGCAGAT CCTGAGCCGC
1501 TACGACATCG CCCTGGTCCA GGAGGTCAGA GACAGCCACC TGA CTG CCGT GGGGAGCTG
1561 CTGGACAACC TCAATCAGGA CGCACCAGAC ACCTATCACT ACGTGGTCAG TGAGCCACTG
1621 GGACGGAACA GCTATAAGGA GCGTACCTG TTCGTGTACA GGCTGACCA GGTGTCTGCG
1681 GTGGACAGCT ACTACTACGA TGATGGCTGC GAGCCCTGCG GGAACGACAC CTTCAACCGA
1741 GAGCCAGCCA TTGTCAGGTT CTTCTCCCGG TTCACAGAGG TCAGGGAGTT TGCCATTGTT
1801 CCCCTGCATG CGGCCCCGGG GGACGCAGTA GCCGAGATCG ACGCTCTCTA TGACGTCTAC
1861 CTGGATGTCC AAGAGAAATG GGGCTTGGAG GACGTCATGT TGATGGGCGA CTTCAATGCG
1921 GGCTGCAGCT ATGTGAGACC CTCCAGTGG TCATCCATCC GCCTGTGGAC AAGCCCCACC
1981 TTCCAGTGGC TGATCCCCGA CAGCGCTGAC ACCACAGCTA CACCCACGCA CTGTGCCTAT
2041 GACAGGATCG TGGTTGCAGG GATGCTGCTC CGAGGGGCGG TTGTTCCCGA CTCGGCTCTT
2101 CCCTTTAACT TCCAGGCTGC CTATGGCCTG AGTGACCAAC TGGCCCCAAG CATCAGTGAC
2161 CACTATCCAG TGGAGGTGAT GCTGAAGTGA

```

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Fig. 9(A)

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```

5'  ATG GGA TGG AGC TGT ATC ATC CTC TTC TTG GTA GCA ACA GCT ACA GGT GTC CAC
    ---
    M  G  W  S  C  I  I  L  F  L  V  A  T  A  T  G  V  H

      63      72      81      90      99      108
TCC CAG GTG CAG CTG GTG CAG TCT GGG GCA GAG GTG AAA AAG CCT GGG GCC TCA
---
S  Q  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  A  S

      117      126      135      144      153      162
GTG AAG GTG TCC TGC AAG GCT TCT GGC TAC ACC TTC AGT GCC TAC TGG ATA GAG
---
V  K  V  S  C  K  A  S  G  Y  T  F  S  A  Y  W  I  E

      171      180      189      198      207      216
TGG GTG CGC CAG GCT CCA GGA AAG GGC CTC GAG TGG GTC GGA GAG ATT TTA CCT
---
W  V  R  Q  A  P  G  K  G  L  E  W  V  G  E  I  L  P

      225      234      243      252      261      270
GGA AGT AAT AAT TCT AGA TAC AAT GAG AAG TTC AAG GGC CGA GTG ACA GTC ACT
---
G  S  N  N  S  R  Y  N  E  K  F  K  G  R  V  T  V  T

      279      288      297      306      315      324
AGA GAC ACA TCC ACA AAC ACA GCC TAC ATG GAG CTC AGC AGC CTG AGG TCT GAG
---
R  D  T  S  T  N  T  A  Y  M  E  L  S  S  L  R  S  E

      333      342      351      360      369      378
GAC ACA GCC GTC TAT TAC TGT GCA AGA TCC TAC GAC TTT GCC TGG TTT GCT TAC
---
D  T  A  V  Y  Y  C  A  R  S  Y  D  F  A  W  F  A  Y

      387      396      405      414      423      432
TGG GGC CAA GGG ACT CTG GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG
---
W  G  Q  G  T  L  V  T  V  S  S  A  S  T  K  G  P  S

      441      450      459      468      477      486
GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC CTG
---
V  F  P  L  A  P  S  S  K  S  T  S  G  G  T  A  A  L

      495      504      513      522      531      540
GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA
---
G  C  L  V  K  D  Y  F  P  E  P  V  T  V  S  W  N  S

      549      558      567      576      585      594
GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA
---
G  A  L  T  S  G  V  H  T  F  P  A  V  L  Q  S  S  G

      603      612      621      630      639      648
CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG
---
L  Y  S  L  S  S  V  V  T  V  P  S  S  S  L  G  T  Q

      657      666      675      684      693      702

```

Fig. 9(B)
(Sheet 1 of 4)

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ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA
-----
T   Y   I   C   N   V   N   H   K   P   S   N   T   K   V   D   K   K

      711      720      729      738      747      756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG TGC CCA GCA CCT
-----
V   E   P   K   S   C   D   K   T   H   T   C   P   P   C   P   A   P

      765      774      783      792      801      810
GAA CTC CTG GGG GGA CCG TCA GTC TTC CTC TTC CCC CCA AAA CCC AAG GAC ACC
-----
E   L   L   G   G   P   S   V   F   L   F   P   P   K   P   K   D   T

      819      828      837      846      855      864
CTC ATG ATC TCC CGG ACC CCT GAG GTC ACA TGC GTG GTG GTG GAC GTG AGC CAC
-----
L   M   I   S   R   T   P   E   V   T   C   V   V   V   D   V   S   H

      873      882      891      900      909      918
GAA GAC CCT GAG GTC AAG TTC AAC TGG TAC GTG GAC GGC GTG GAG GTG CAT AAT
-----
E   D   P   E   V   K   F   N   W   Y   V   D   G   V   E   V   H   N

      927      936      945      954      963      972
GCC AAG ACA AAG CCG CGG GAG GAG CAG TAC AAC AGC ACG TAC CGT GTG GTC AGC
-----
A   K   T   K   P   R   E   E   Q   Y   N   S   T   Y   R   V   V   S

      981      990      999      1008      1017      1026
GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAT GGC AAG GAG TAC AAG TGC AAG
-----
V   L   T   V   L   H   Q   D   W   L   N   G   K   E   Y   K   C   K

      1035      1044      1053      1062      1071      1080
GTC TCC AAC AAA GCC CTC CCA GCC CCC ATC GAG AAA ACC ATC TCC AAA GCC AAA
-----
V   S   N   K   A   L   P   A   P   I   E   K   T   I   S   K   A   K

      1089      1098      1107      1116      1125      1134
GGG CAG CCC CGA GAA CCA CAG GTG TAC ACC CTG CCC CCA TCC CGG GAT GAG CTG
-----
G   Q   P   R   E   P   Q   V   Y   T   L   P   P   S   R   D   E   L

      1143      1152      1161      1170      1179      1188
ACC AAG AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAT CCC AGC GAC
-----
T   K   N   Q   V   S   L   T   C   L   V   K   G   F   Y   P   S   D

      1197      1206      1215      1224      1233      1242
ATC GCC GTG GAG TGG GAG AGC AAT GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG
-----
I   A   V   E   W   E   S   N   G   Q   P   E   N   N   Y   K   T   T

      1251      1260      1269      1278      1287      1296
CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC AAG CTC ACC GTG
-----
P   P   V   L   D   S   D   G   S   F   F   L   Y   S   K   L   T   V

      1305      1314      1323      1332      1341      1350
GAC AAG AGC AGG TGG CAG CAG GGG AAC GTC TTC TCA TGC TCC GTG ATG CAT GAG
-----
D   K   S   R   W   Q   Q   G   N   V   P   S   C   S   V   M   H   E

```

Fig. 9(B)
(Sheet 2 of 4)

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1359	1368	1377	1386	1395	1404
GCT CTG CAC AAC CAC TAC ACG CAG AAG AGC CTC TCC CTG TCC CCG GGG AGC GGC					

A L H N H Y T Q K S L S L S P	<u>G S G</u>				

1413	1422	1431	1440	1449	1458
GGG CTG AAG ATC GCA GCC TTC AAC ATC CAG ACA TTT GGG GAG ACC AAG ATG TCC					

<u>G</u> L K I A A F N I Q T F G E T K M S					

1467	1476	1485	1494	1503	1512
AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG ATC CTG AGC CGC TAC GAC ATC GCC					

N A T L V S Y I V Q I L S R Y D I A					

1521	1530	1539	1548	1557	1566
CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG ACT GCC GTG GGG AAG CTG CTG GAC					

L V Q E V R D S H L T A V G K L L D					

1575	1584	1593	1602	1611	1620
AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT CAC TAC GTG GTC AGT GAG CCA CTG					

N L N Q D A P D T Y H Y V V S E P L					

1629	1638	1647	1656	1665	1674
GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG TTC GTG TAC AGG CCT GAC CAG GTG					

G R N S Y K E R Y L F V Y R P D Q V					

1683	1692	1701	1710	1719	1728
TCT GCG GTG GAC AGC TAC TAC TAC GAT GAT GGC TGC GAG CCC TGC GGG AAC GAC					

S A V D S Y Y Y D D G C E P C G N D					

1737	1746	1755	1764	1773	1782
ACC TTC AAC CGA GAG CCA GCC ATT GTG AGG TTC TTC TCC CGG TTC ACA GAG GTC					

T F N R E P A I V R F F S R F T E V					

1791	1800	1809	1818	1827	1836
AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG GCC CCG GGG GAC GCA GTA GCC GAG					

R E F A I V P L H A A P G D A V A E					

1845	1854	1863	1872	1881	1890
ATC GAC GCT CTC TAT GAC GTC TAC CTG GAT GTC CAA GAG AAA TGG GGC TTG GAG					

I D A L Y D V Y L D V Q E K W G L E					

1899	1908	1917	1926	1935	1944
GAC GTC ATG TTG ATG GGC GAC TTC AAT GCG GGC TGC AGC TAT GTG AGA CCC TCC					

D V M L M G D F N A G C S Y V R P S					

1953	1962	1971	1980	1989	1998
CAG TGG TCA TCC ATC CGC CTG TGG ACA AGC CCC ACC TTC CAG TGG CTG ATC CCC					

Q W S S I R L W T S P T F Q W L I P					

2007	2016	2025	2034	2043	2052
GAC AGC GCT GAC ACC ACA GCT ACA CCC ACG CAC TGT GCC TAT GAC AGG ATC GTG					

D S A D T T A T P T H C A Y D R I V					

Fig. 9(B)
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2061	2070	2079	2088	2097	2106
GTT GCA GGG ATG CTG CTC CGA GGG GCC GTT GTT CCC GAC TCG GCT CTT CCC TTT					

V A G M L L R G A V V P D S A L P F					
2115	2124	2133	2142	2151	2160
AAC TTC CAG GCT GCC TAT GGC CTG AGT GAC CAA CTG GCC CAA GCC ATC AGT GAC					

N F Q A A Y G L S D Q L A Q A I S D					
2169	2178	2187			
CAC TAT CCA GTG GAG GTG ATG CTG AAG TGA 3'					

H Y P V E V M L K *					

Fig. 9(B)
(Sheet 4 of 4)

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pAS37

LOCUS PAS37.DNA 2226 bp 2196 bp 2196 bp DNA 14-AUG-1998

DEFINITION HUMANISED HMFG1 heavy chain fused to human DNase construct 37

DEFINITION Clone 16.4.2 (same as hcdnasel.dna template file) plus NLS

REFERENCE

AUTHORS VERHOEYEN ET AL

TITLE CONSTRUCTION OF RESHAPED HMFG1 etc

JOURNAL IMMUNOL. (1993):78, 364-370

COMMENT Human DNase sequence is modified as a result of oligo assembly (mhdnase.dna)

COMMENT The fusion was made using overlapping oligos AS79 and AS80

FEATURES AA RESIDUE 235 HAS NOT BEEN CHANGED TO KABAT (I.E. V TO A)

FEATURES Residue 963 is G > T leading to silent mutation in all clones

SITES Note

BASE COUNT 511 a 683 c 619 g 413 t

ORIGIN ?

```

1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCACTGCC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGGTGC GTGGAAC TCA
541 GGCGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAAAC TC ACACATGCCC ACCGTGCCCC GCACCTGAAC TCCTGGGGGG ACCGTCAGTC
781 TTCCTCTTCC CCCCCAAACC CAAGGACACC CTCATGATCT CCCGACCCC TGAGGTCACA
841 TGCGTGGTGG TGGACGTGAG CCACGAAGAC CCTGAGGTCA AGTTCAACTG GTACGTGGAC
901 GCGGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG AGCAGTACAA CAGCACGTAC
961 CGTGTGGTCA GCGTCCTCAC CGTCCTGCAC CAGGACTGGC TGAATGGCAA GGAGTACAAG
1021 TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA AAACCATCTC CAAAGCCAAA
1081 GGGCAGCCCC GAGAACCACA GGTGTACACC CTGCCCCCAT CCCGGGATGA GCTGACCAAAG
1141 AACCAGGTCA GCCTGACCTG CCTGGTCAAA GGCTTCTATC CCAGCGACAT CGCCGTGGAG
1201 TGGGAGAGCA ATGGGCAGCC GGAGAACAAC TACAAGACCA CGCCTCCCGT GCTGGACTCC
1261 GACGGCTCCT TCTTCTCTA CAGCAAGCTC ACCGTGGACA AGAGCAGGTG GCAGCAGGGG
1321 AACGTCTTCT CATGCTCCGT GATGCATGAG GCTCTGCACA ACCACTACAC GCAGAAGAGC
1381 CTCTCCCTGT CTCCGGGTAA AGGGAGCGGC GGGCTGAAGA TCGCAGCCTT CAACATCCAG
1441 ACATTTGGGG AGACCAAGAT GTCCAATGCC ACCCTCGTCA GCTACATTGT GCAGATCCTG
1501 AGCCGCTACG ACATCGCCCT GGTCCAGGAG GTCAGAGACA GCCACCTGAC TGCCGTGGGG
1561 AAGCTGCTGG ACAACCTCAA TCAGGACGCA CCAGACACCT ATCACTACGT GGTCAGTGAG
1621 CCACTGGGAC GGAACAGCTA TAAGGAGCGC TACCTGTTCC TGTACAGGCC TGACCAGGTG
1681 TCTGCGGTGG ACAGCTACTA CTACGATGAT GGCTGCGAGC CCTGCGGGAA CGACACCTTC
1741 AACCAGAGAG CAGCCATTGT CAGGTTCTTC TCCCAGTTCA CAGAGGTCAG GGAGTTTGCC
1801 ATTGTTCCCC TGCATGCGGC CCCGGGGGAC GCAGTAGCCG AGATCGACGC TCTCTATGAC
1861 GTCTACCTGG ATGTCCAAGA GAAATGGGCG TTGGAGGACG TCATGTTGAT GGGCGACTTC
1921 AATGCGGGCT GCAGCTATGT GAGACCCTCC CAGTGGTCAT CCATCCGCCT GTGGACAAGC
1981 CCCACCTTCC AGTGGCTGAT CCCCAGACGC GCTGACACCA CAGCTACACC CACGCACTGT
2041 GCCTATGACA GGATCGTGGT TGCAGGGATG CTGCTCCGAG GGGCCGTTGT TCCCGACTCG
2101 GCTCTTCCCT TTAACCTCCA GGCTGCCTAT GGCTGAGTG ACCAACTGGC CCAAGCCATC
2161 AGTGACCACT ATCCAGTGGA GGTGATGCTG AAGGGGGGCG GACCCAAAAA GAAGCGCAAG
2221 GTTTGA

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NLS

Fig. 10(A)

5'	9				18				27				36				45				54			
	ATG	GGA	TGG	AGC	TGT	ATC	ATC	CTC	TTC	TTG	GTA	GCA	ACA	GCT	ACA	GGT	GTC	CAC						
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---						
	M	G	W	S	C	I	I	L	F	L	V	A	T	A	T	G	V	H						
	63				72				81				90				99				108			
	TCC	CAG	GTG	CAG	CTG	GTG	CAG	TCT	GGG	GCA	GAG	GTG	AAA	AAG	CCT	GGG	GCC	TCA						
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---						
	S	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S						
	117				126				135				144				153				162			
	GTG	AAG	GTG	TCC	TGC	AAG	GCT	TCT	GGC	TAC	ACC	TTC	AGT	GCC	TAC	TGG	ATA	GAG						
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---						
	V	K	V	S	C	K	A	S	G	Y	T	F	S	A	Y	W	I	E						
	171				180				189				198				207				216			
	TGG	GTG	CGC	CAG	GCT	CCA	GGA	AAG	GGC	CTC	GAG	TGG	GTC	GGA	GAG	ATT	TTA	CCT						
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---						
	W	V	R	Q	A	P	G	K	G	L	E	W	V	G	E	I	L	P						
	225				234				243				252				261				270			
	GGA	AGT	AAT	AAT	TCT	AGA	TAC	AAT	GAG	AAG	TTC	AAG	GGC	CGA	GTG	ACA	GTC	ACT						
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---						
	G	S	N	N	S	R	Y	N	E	K	F	K	G	R	V	T	V	T						
	279				288				297				306				315				324			
	AGA	GAC	ACA	TCC	ACA	AAC	ACA	GCC	TAC	ATG	GAG	CTC	AGC	AGC	CTG	AGG	TCT	GAG						
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---						
	R	D	T	S	T	N	T	A	Y	M	E	L	S	S	L	R	S	E						
	333				342				351				360				369				378			
	GAC	ACA	GCC	GTC	TAT	TAC	TGT	GCA	AGA	TCC	TAC	GAC	TTT	GCC	TGG	TTT	GCT	TAC						
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---						
	D	T	A	V	Y	Y	C	A	R	S	Y	D	F	A	W	F	A	Y						
	387				396				405				414				423				432			
	TGG	GGC	CAA	GGG	ACT	CTG	GTC	ACA	GTC	TCC	TCA	GCC	TCC	ACC	AAG	GGC	CCA	TCG						
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---						
	W	G	Q	G	T	L	V	T	V	S	S	A	S	T	K	G	P	S						
	441				450				459				468				477				486			
	GTC	TTC	CCC	CTG	GCA	CCC	TCC	TCC	AAG	AGC	ACC	TCT	GGG	GGC	ACA	GCG	GCC	CTG						
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---						
	V	F	P	L	A	P	S	S	K	S	T	S	G	G	T	A	A	L						
	495				504				513				522				531				540			
	GGC	TGC	CTG	GTC	AAG	GAC	TAC	TTC	CCC	GAA	CCG	GTG	ACG	GTG	TCG	TGG	AAC	TCA						
	---	---	---	---	---	---	---</																	

Fig. 10(B)
(Sheet 1 of 4)

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ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA
---
T Y I C N V N H K P S N T K V D K K

711 720 729 738 747 756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG TGC CCA GCA CCT
---
V E P K S C D K T H T C P P C P A P

765 774 783 792 801 810
GAA CTC CTG GGG GGA CCG TCA GTC TTC CTC TTC CCC CCA AAA CCC AAG GAC ACC
---
E L L G G P S V F L F P P K P K D T

819 828 837 846 855 864
CTC ATG ATC TCC CGG ACC CCT GAG GTC ACA TGC GTG GTG GTG GAC GTG AGC CAC
---
L M I S R T P E V T C V V V D V S H

873 882 891 900 909 918
GAA GAC CCT GAG GTC AAG TTC AAC TGG TAC GTG GAC GGC GTG GAG GTG CAT AAT
---
E D P E V K F N W Y V D G V E V H N

927 936 945 954 963 972
GCC AAG ACA AAG CCG CGG GAG GAG CAG TAC AAC AGC ACG TAC CGT GTG GTC AGC
---
A K T K P R E E Q Y N S T Y R V V S

981 990 999 1008 1017 1026
GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAT GGC AAG GAG TAC AAG TGC AAG
---
V L T V L H Q D W L N G K E Y K C K

1035 1044 1053 1062 1071 1080
GTC TCC AAC AAA GCC CTC CCA GCC CCC ATC GAG AAA ACC ATC TCC AAA GCC AAA
---
V S N K A L P A P I E K T I S K A K

1089 1098 1107 1116 1125 1134
GGG CAG CCC CGA GAA CCA CAG GTG TAC ACC CTG CCC CCA TCC CGG GAT GAG CTG
---
G Q P R E P Q V Y T L P P S R D E L

1143 1152 1161 1170 1179 1188
ACC AAG AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAT CCC AGC GAC
---
T K N Q V S L T C L V K G F Y P S D

1197 1206 1215 1224 1233 1242
ATC GCC GTG GAG TGG GAG AGC AAT GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG
---
I A V E W E S N G Q P E N N Y K T T

1251 1260 1269 1278 1287 1296
CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC AAG CTC ACC GTG
---
P P V L D S D G S F F L Y S K L T V

1305 1314 1323 1332 1341 1350
GAC AAG AGC AGG TGG CAG CAG GGG AAC GTC TTC TCA TGC TCC GTG ATG CAT GAG
---
D K S R W Q Q G N V F S C S V M H E

```

Fig. 10(B)
(Sheet 2 of 4)

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1359	1368	1377	1386	1395	1404
GCT CTG CAC AAC CAC TAC ACG CAG AAG AGC CTC TCC CTG TCT CCG GGT AAA GGG					
A L H N H Y T Q K S L S L S P G K <u>G</u>					
1413	1422	1431	1440	1449	1458
AGC GGC GGG CTG AAG ATC GCA GCC TTC AAC ATC CAG ACA TTT GGG GAG ACC AAG					
<u>S G G</u> L K I A A F N I Q T F G E T K					
1467	1476	1485	1494	1503	1512
ATG TCC AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG ATC CTG AGC CGC TAC GAC					
M S N A T L V S Y I V Q I L S R Y D					
1521	1530	1539	1548	1557	1566
ATC GCC CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG ACT GCC GTG GGG AAG CTG					
I A L V Q E V R D S H L T A V G K L					
1575	1584	1593	1602	1611	1620
CTG GAC AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT CAC TAC GTG GTC AGT GAG					
L D N L N Q D A P D T Y H Y V V S E					
1629	1638	1647	1656	1665	1674
CCA CTG GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG TTC GTG TAC AGG CCT GAC					
P L G R N S Y K E R Y L F V Y R P D					
1683	1692	1701	1710	1719	1728
CAG GTG TCT GCG GTG GAC AGC TAC TAC TAC GAT GAT GGC TGC GAG CCC TGC GGG					
Q V S A V D S Y Y Y D D G C E P C G					
1737	1746	1755	1764	1773	1782
AAC GAC ACC TTC AAC CGA GAG CCA GCC ATT GTC AGG TTC TTC TCC CGG TTC ACA					
N D T F N R E P A I V R F F S R F T					
1791	1800	1809	1818	1827	1836
GAG GTC AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG GCC CCG GGG GAC GCA GTA					
E V R E F A I V P L H A A P G D A V					
1845	1854	1863	1872	1881	1890
GCC GAG ATC GAC GCT CTC TAT GAC GTC TAC CTG GAT GTC CAA GAG AAA TGG GGC					
A E I D A L Y D V Y L D V Q E K W G					
1899	1908	1917	1926	1935	1944
TTG GAG GAC GTC ATG TTG ATG GGC GAC TTC AAT GCG GGC TGC AGC TAT GTG AGA					
L E D V M L M G D F N A G C S Y V R					
1953	1962	1971	1980	1989	1998
CCC TCC CAG TGG TCA TCC ATC CGC CTG TGG ACA AGC CCC ACC TTC CAG TGG CTG					
P S Q W S S I R L W T S P T F Q W L					
2007	2016	2025	2034	2043	2052
ATC CCC GAC AGC GCT GAC ACC ACA GCT ACA CCC ACG CAC TGT GCC TAT GAC AGG					
I P D S A D T T A T P T H C A Y D R					

Fig. 10(B)
(Sheet 3 of 4)

2061			2070			2079			2088			2097			2106		
ATC	GTG	GTT	GCA	GGG	ATG	CTG	CTC	CGA	GGG	GCC	GTT	GTT	CCC	GAC	TCG	GCT	CTT
I	V	V	A	G	M	L	L	R	G	A	V	V	P	D	S	A	L
2115			2124			2133			2142			2151			2160		
CCC	TTT	AAC	TTC	CAG	GCT	GCC	TAT	GGC	CTG	AGT	GAC	CAA	CTG	GCC	CAA	GCC	ATC
P	F	N	F	Q	A	A	Y	G	L	S	D	Q	L	A	Q	A	I
2169			2178			2187			2196			2205			2214		
AGT	GAC	CAC	TAT	CCA	GTG	GAG	GTG	ATG	CTG	AAG	GGG	GGC	GGA	CCC	AAA	AAG	AAG
S	D	H	Y	P	V	E	V	M	L	K	<u>G</u>	<u>G</u>	<u>G</u>	<u>P</u>	<u>K</u>	<u>K</u>	<u>K</u>
2223																	
CGC AAG GTT TGA 3'																	
<div> <div>R</div> <div>K</div> <div>V</div> <div>*</div> </div>																	

Fig. 10(B)
(Sheet 4 of 4)

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pAS38

LOCUS PAS38.DNA 2223 bp 2193 bp DNA 14-AUG-1998
 DEFINITION HUMANISED HMFG1 heavy chain fused to human DNase construct 38
 DEFINITION Clone 17.12.1 with silent K to K mutation (1398 A > G)+NLS
 REFERENCE
 AUTHORS VERHOEYEN ET AL
 TITLE CONSTRUCTION OF RESHAPED HMFG1 etc
 JOURNAL IMMUNOL. (1993):78, 364-370
 COMMENT Human DNase sequence is modified as a result of oligo assembly (mhdnase.dna)
 COMMENT The fusion was made using overlapping oligos AS81 and AS82
 FEATURES AA RESIDUE 235 HAS NOT BEEN CHANGED TO KABAT (I.E. V TO A)
 FEATURES Residue 963 is G > T leading to silent mutation in all clones
 FEATURES In 17.12.1 residue 1398 is A > G (silent K to K mutation)
 SITES Note
 BASE COUNT 510 a 683 c 618 g 412 t
 ORIGIN ?

```

1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTAGTGCC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCAGACGG
481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAAGTCA
541 GCGGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAAATC ACACATGCCC ACCGTGCCCA GCACCTGAAC TCCTGGGGGG ACCGTCAGTC
781 TTCCTCTTCC CCCCCAAACC CAAGGACACC CTCATGATCT CCCGGACCCC TGAGGTGACA
841 TGCGTGGTGG TGGACGTGAG CCACGAAGAC CCTGAGGTCA AGTTCAACTG GTACGTGGAC
901 GCGGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG AGCAGTACAA CAGCAGGTAC
961 CGTGTGGTCA GCGTCTCAC CGTCTGCAC CAGGACTGGC TGAATGGCAA GGAGTACAAG
1021 TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA AAACCATCTC CAAAGCCAAA
1081 GGGCAGCCCC GAGAACCACA GGTGTACACC CTGCCCCAT CCCGGGATGA GCTGACCAAG
1141 AACCAGGTCA GCCTGACCTG CCTGGTCAAA GGCTTCTATC CCAGCGACAT CGCCGTGGAG
1201 TGGGAGAGCA ATGGGCAGCC GGAGAACAAC TACAAGACCA CGCCTCCCGT GCTGGACTCC
1261 GACGGCTCCT TCTTCTCTA CAGCAGCTC ACCGTGGACA AGAGCAGGTG GCAGCAGGGG
1321 AACGTCTTCT CATGCTCCGT GATGCATGAG GCTCTGCACA ACCACTACAC GCAGAAGAGC
1381 CTCTCCCTGT CTCCGAAGGG GAGCGGCGGG CTGAAGATCG CAGCCTTCAA CATCCAGACA
1441 TTTGGGGAGA CCAAGATGTC CAATGCCACC CTCGTCAGCT ACATTGTGCA GATCCTGAGC
1501 CGCTACGACA TCGCCCTGGT CCAGGAGGTC AGAGACAGCC ACCTGACTGC CGTGGGGAAG
1561 CTGCTGGACA ACCTCAATCA GGACGCACCA GACACCTATC ACTACGTGGT CAGTGAGCCA
1621 CTGGGACGGA ACAGCTATAA GGAGCGCTAC CTGTTCGTGT ACAGCGCTGA CCAGGTGTCT
1681 GCGGTGGACA GCTACTACTA CGATGATGGC TCGAGGCCCT GCGGGAACGA CACCTTCAAC
1741 CGAGAGCCAG CCATTGTCAG GTTCTTCTCC CGGTTACAG AGGTCAGGGA GTTTGCCATT
1801 GTTCCCCTGC ATGCGGCCCC GGGGACGCA GTAGCCGAGA TCGACGCTCT CTATGACGTC
1861 TACCTGGATG TCCAAGAGAA ATGGGGCTTG GAGGACGTCA TGTTGATGGG CGACTTCAAT
1921 GCGGGCTGCA GCTATGTGAG ACCCTCCCAG TGGTCATCCA TCCGCCTGTG GACAAGCCCC
1981 ACCTTCCAGT GGCTGATCCC CGACAGCGCT GACACCCAG CTACACCCAG GCACCTGGCC
2041 TATGACAGGA TCGTGTTGC AGGGATGCTG CTCCGAGGGG CCGTTGTTCC CGACTCGGCT
2101 CTTCCCTTTA ACTTCCAGGC TGCCTATGGC CTGAGTGACC AACTGGCCCA AGCCATCAGT
2161 GACCACTATC CAGTGGAGGT GATGCTGAAG GGGGGCGGAC CCAAAAGAA GCGCAAGGTT
2221 TGA

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NLS

Fig. 11(A)

	9				18				27				36				45				
5'	ATG	GGA	TGG	AGC	TGT	ATC	ATC	CTC	TTC	TTG	GTA	GCA	ACA	GCT	ACA	GGT	GTC	CAC	5'		
	M	G	W	S	C	I	I	L	F	L	V	A	T	A	T	G	V	H			
			63				72			81			90			99		108			
	TCC	CAG	GTG	CAG	CTG	GTG	CAG	TCT	GGG	GCA	GAG	GTG	AAA	AAG	CCT	GGG	GCC	TCA			
	S	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S			
			117				126			135			144			153		162			
	GTG	AAG	GTG	TCC	TGC	AAG	GCT	TCT	GGC	TAC	ACC	TTC	AGT	GCC	TAC	TGG	ATA	GAG			
	V	K	V	S	C	K	A	S	G	Y	T	F	S	A	Y	W	I	E			
			171				180			189			198			207		216			
	TGG	GTG	CGC	CAG	GCT	CCA	GGA	AAG	GGC	CTC	GAG	TGG	GTC	GGA	GAG	ATT	TTA	CCT			
	W	V	R	Q	A	P	G	K	G	L	E	W	V	G	E	I	L	P			
			225				234			243			252			261		270			
	GGA	AGT	AAT	AAT	TCT	AGA	TAC	AAT	GAG	AAG	TTC	AAG	GGC	CGA	GTG	ACA	GTC	ACT			
	G	S	N	N	S	R	Y	N	E	K	F	K	G	R	V	T	V	T			
			279				288			297			306			315		324			
	AGA	GAC	ACA	TCC	ACA	AAC	ACA	GCC	TAC	ATG	GAG	CTC	AGC	AGC	CTG	AGG	TCT	GAG			
	R	D	T	S	T	N	T	A	Y	M	E	L	S	S	L	R	S	E			
			333				342			351			360			369		378			
	GAC	ACA	GCC	GTC	TAT	TAC	TGT	GCA	AGA	TCC	TAC	GAC	TTT	GCC	TGG	TTT	GCT	TAC			
	D	T	A	V	Y	Y	C	A	R	S	Y	D	F	A	W	F	A	Y			
			387				396			405			414			423		432			
	TGG	GGC	CAA	GGG	ACT	CTG	GTC	ACA	GTC	TCC	TCA	GCC	TCC	ACC	AAG	GGC	CCA	TGG			
	W	G	Q	G	T	L	V	T	V	S	S	A	S	T	K	G	P	S			
			441				450			459			468			477		486			
	GTC	TTC	CCC	CTG	GCA	CCC	TCC	TCC	AAG	AGC	ACC	TCT	GGG	GGC	ACA	GCG	GCC	CTG			
	V	F	P	L	A	P	S	S	K	S	T	S	G	G	T	A	A	L			
			495				504			513			522			531		540			
	GGC	TGC	CTG	GTC	AAG	GAC	TAC	TTC	CCC	GAA	CCG	GTG	ACG	GTG	TGG	TGG	AAC	TCA			
	G	C	L	V	K	D	Y	F	P	E	P	V	T	V	S	W	N	S			
			549				558			567			576			585		594			
	GGC	GCC	CTG	ACC	AGC	GGC	GTG	CAC	ACC	TTC	CCG	GCT	GTC	CTA	CAG	TCC	TCA	GGA			
	G	A	L	T	S	G	V	H	T	F	P	A	V	L	Q	S	S	G			
			603				612			621			630			639		648			
	CTC	TAC	TCC	CTC	AGC	AGC	GTG	GTG	ACC	GTG	CCC	TCC	AGC	AGC	TTG	GGC	ACC	CAG			
	L	Y	S	L	S	S	V	V	T	V	P	S	S	S	L	G	T	Q			
</																					

Fig. 11(B)
(Sheet 1 of 4)

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ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA
-----
T   Y   I   C   N   V   N   H   K   P   S   N   T   K   V   D   K   K

      711      720      729      738      747      756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG TGC CCA GCA CCT
-----
V   E   P   K   S   C   D   K   T   H   T   C   P   P   C   P   A   P

      765      774      783      792      801      810
GAA CTC CTG GGG GGA CCG TCA GTC TTC CTC TTC CCC CCA AAA CCC AAG GAC ACC
-----
E   L   L   G   G   P   S   V   F   L   F   P   P   K   P   K   D   T

      819      828      837      846      855      864
CTC ATG ATC TCC CGG ACC CCT GAG GTC ACA TGC GTG GTG GTG GAC GTG AGC CAC
-----
L   M   I   S   R   T   P   E   V   T   C   V   V   V   D   V   S   H

      873      882      891      900      909      918
GAA GAC CCT GAG GTC AAG TTC AAC TGG TAC GTG GAC GGC GTG GAG GTG CAT AAT
-----
E   D   P   E   V   K   F   N   W   Y   V   D   G   V   E   V   H   N

      927      936      945      954      963      972
GCC AAG ACA AAG CCG CGG GAG GAG CAG TAC AAC AGC ACG TAC CGT GTG GTC AGC
-----
A   K   T   K   P   R   E   E   Q   Y   N   S   T   Y   R   V   V   S

      981      990      999      1008      1017      1026
GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAT GGC AAG GAG TAC AAG TGC AAG
-----
V   L   T   V   L   H   Q   D   W   L   N   G   K   E   Y   K   C   K

      1035      1044      1053      1062      1071      1080
GTC TCC AAC AAA GCC CTC CCA GCC CCC ATC GAG AAA ACC ATC TCC AAA GCC AAA
-----
V   S   N   K   A   L   P   A   P   I   E   K   T   I   S   K   A   K

      1089      1098      1107      1116      1125      1134
GGG CAG CCC CGA GAA CCA CAG GTG TAC ACC CTG CCC CCA TCC CGG GAT GAG CTG
-----
G   Q   P   R   E   P   Q   V   Y   T   L   P   P   S   R   D   E   L

      1143      1152      1161      1170      1179      1188
ACC AAG AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAT CCC AGC GAC
-----
T   K   N   Q   V   S   L   T   C   L   V   K   G   F   Y   P   S   D

      1197      1206      1215      1224      1233      1242
ATC GCC GTG GAG TGG GAG AGC AAT GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG
-----
I   A   V   E   W   E   S   N   G   Q   P   E   N   N   Y   K   T   T

      1251      1260      1269      1278      1287      1296
CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC AAG CTC ACC GTG
-----
P   P   V   L   D   S   D   G   S   F   F   L   Y   S   K   L   T   V

      1305      1314      1323      1332      1341      1350
GAC AAG AGC AGG TGG CAG CAG GGG AAC GTC TTC TCA TGC TCC GTG ATG CAT GAG
-----
D   K   S   R   W   Q   Q   G   N   V   F   S   C   S   V   M   H   E

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Fig. 11(B)
(Sheet 2 of 4)

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1359	1368	1377	1386	1395	1404
GCT CTG CAC AAC CAC TAC ACG CAG AAG AGC CTC TCC CTG TCT CCG AAG GGG AGC					
A L H N H Y T Q K S L S L S P K <u>G S</u>					
1413	1422	1431	1440	1449	1458
GGC GGG CTG AAG ATC GCA GCC TTC AAC ATC CAG ACA TTT GGG GAG ACC AAG ATG					
<u>G G</u> L K I A A F N I Q T F G E T K M					
1467	1476	1485	1494	1503	1512
TCC AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG ATC CTG AGC CGC TAC GAC ATC					
S N A T L V S Y I V Q I L S R Y D I					
1521	1530	1539	1548	1557	1566
GCC CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG ACT GCC GTG GGG AAG CTG CTG					
A L V Q E V R D S H L T A V G K L L					
1575	1584	1593	1602	1611	1620
GAC AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT CAC TAC GTG GTC AGT GAG CCA					
D N L N Q D A P D T Y H Y V V S E P					
1629	1638	1647	1656	1665	1674
CTG GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG TTC GTG TAC AGG CCT GAC CAG					
L G R N S Y K E R Y L F V Y R P D Q					
1683	1692	1701	1710	1719	1728
GTG TCT GCG GTG GAC AGC TAC TAC TAC GAT GAT GGC TGC GAG CCC TGC GGG AAC					
V S A V D S Y Y Y D D G C E P C G N					
1737	1746	1755	1764	1773	1782
GAC ACC TTC AAC CGA GAG CCA GCC ATT GTC AGG TTC TTC TCC CGG TTC ACA GAG					
D T F N R E P A I V R F F S R F T E					
1791	1800	1809	1818	1827	1836
GTG AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG GCC CCG GGG GAC GCA GTA GCC					
V R E F A I V P L H A A P G D A V A					
1845	1854	1863	1872	1881	1890
GAG ATC GAC GCT CTC TAT GAC GTC TAC CTG GAT GTC CAA GAG AAA TGG GGC TTG					
E I D A L Y D V Y L D V Q E K W G L					
1899	1908	1917	1926	1935	1944
GAG GAC GTC ATG TTG ATG GGC GAC TTC AAT GCG GGC TGC AGC TAT GTG AGA CCC					
E D V M L M G D F N A G C S Y V R P					
1953	1962	1971	1980	1989	1998
TCC CAG TGG TCA TCC ATC CGC CTG TGG ACA AGC CCC ACC TTC CAG TGG CTG ATC					
S Q W S S I R L W T S P T F Q W L I					
2007	2016	2025	2034	2043	2052
CCC GAC AGC GCT GAC ACC ACA GCT ACA CCC ACG CAC TGT GCC TAT GAC AGG ATC					
P D S A D T T A T P T H C A Y D R I					

Fig. 11(C)
(Sheet 3 of 4)

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2061	2070	2079	2088	2097	2106
GTG GTT GCA GGG ATG CTG CTC CGA GGG GCC GTT GTT CCC GAC TCG GCT CTT CCC					

V V A G M L L R G A V V P D S A L P					
2115	2124	2133	2142	2151	2160
TTT AAC TTC CAG GCT GCC TAT GGC CTG AGT GAC CAA CTG GCC CAA GCC ATC AGT					

F N F Q A A Y G L S D Q L A Q A I S					
2169	2178	2187	2196	2205	2214
GAC CAC TAT CCA GTG GAG GTG ATG CTG AAG GGG GGC GGA CCC AAA AAG AAG CGC					

D H Y P V E V M L K	<u>G G G P K K K R</u>				

2223					
AAG GTT TGA 3'					

K V *					
=====					

Fig. 11(D)
(Sheet 4 of 4)

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pAS39

LOCUS PAS39.DNA 2220 bp 2190 bp DNA 14-AUG-1998

DEFINITION HUMANISED HMFG1 heavy chain fused to human DNase - construct 39

DEFINITION Clone 18.24.1 with residue 1392 T > C +NLS

REFERENCE

AUTHORS VERHOEYEN ET AL

TITLE CONSTRUCTION OF RESHAPED HMFG1 etc

JOURNAL IMMUNOL. (1993):78, 364-370

COMMENT Human DNase sequence is modified as a result of oligo assembly (mhdnase.dna)

COMMENT The fusion was made using overlapping oligos AS83 and AS84

FEATURES AA RESIDUE 235 HAS NOT BEEN CHANGED TO KABAT (I.E. V TO A)

FEATURES Residue 963 is G > T leading to silent mutation in all clones

FEATURES Residue 1392 T > C silent S to S mutation

SITES Note

BASE COUNT 508 a 684 c 617 g 411 t

ORIGIN ?

```

1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCAAGTGC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCTGGT TTGCTTACTG GGGCCAAAGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTG GTGGAAGTCA
541 GCGGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAAATC ACACATGCCC ACCGTGCCCA GCACCTGAAC TCCTGGGGGG ACCGTCAATC
781 TTCTCTTCC CCCCCAAACC CAAGGACACC CTCATGATCT CCCGGACCCC TGAGGTACA
841 TGCGTGGTGG TGGACGTGAG CCACGAAGAC CCTGAGGTCA AGTTCAACTG GTACGTGGAC
901 GCGGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG AGCAGTACAA CAGCACGTAC
961 CGTGTGGTCA GCGTCTTCAC CGTCTGCAC CAGGACTGGC TGAATGGCAA GGAGTACAAG
1021 TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA AAACCATCTC CAAAGCCAAA
1081 GGGCAGCCCC GAGAACCACA GGTGTACACC CTGCCCCCAT CCCGGGATGA GCTGACCAAG
1141 AACCAGGTCA GCCTGACCTG CCTGGTCAAA GGCTTCTATC CCAGCGACAT CGCCGTGGAG
1201 TGGGAGAGCA ATGGGCAGCC GGAGAACAC TACAAGACCA CGCCTCCCGT GCTGGACTCC
1261 GACGGCTCCT TCTTCTCTA CAGCAAGCTC ACCGTGGACA AGAGCAGGTG GCAGCAGGGG
1321 AACGTCTTCT CATGCTCCGT GATGCATGAG GCTCTGCACA ACCACTACAC GCAGAAGAGC
1381 CTCTCCCTGT CcCCGGGGAG CGGCGGGCTG AAGATCGCAG CCTTCAACAT CCAGACATTT
1441 GGGGAGACCA AGATGTCCAA TGCCACCCTC GTCAGCTAaA TTGTGCAGAT CCTGAGCCCG
1501 TACGACATCG CCCTGGTCCA GGAGGTGAGA GACAGCCACC TGACTGCCGT GGGGAAGCTG
1561 CTGGACAACC TCAATCAGGA CGCACCAGAC ACCTATCACT ACCTGGTCAG TGAGCCACTG
1621 GGACGGAACA GCTATAAGGA GCGCTACCTG TTCGTGTACA GGCTGACCA GGTGTCTGCG
1681 GTGGACAGCT ACTACTACGA TGATGGCTGC GAGCCCTGCG GGAACGACAC CTTCAACCGA
1741 GAGCCAGCCA TTGTCAGGTT CTTCTCCCGG TTCACAGAGG TCAGGGAGTT TGCCATTGTT
1801 CCCCTGCATG CGCCCCGGG GGACGCAGTA GCCGAGATCG ACCTCTCTA TGACGTCTAC
1861 CTGGATGTCC AAGAGAAATG GGGCTTGGAG GACGTCATGT TGATGGGCGA CTTCAATGCG
1921 GGCTGCAGCT ATGTGAGACC CTCCCAGTGG TCATCCATCC GCCTGTGCAG AAGCCCCACC
1981 TTCCAGTGGC TGATCCCCGA CAGCGCTGAC ACCACAGCTA CACCCAGCGA CTGTGCCTAT
2041 GACAGGATCG TGGTTGCAGG GATGCTGCTC CGAGGGGCGG TTGTTCCCGA CTCGGCTCTT
2101 CCCTTTAACT TCCAGGCTGC CTATGGCCTG AGTGACCAAC TGGCCCAAGC CATCAGTGAC
2161 CACTATCCAG TGGAGGTGAT GCTGAAGGGG GGCGGACCCA AAAAGAAGCG CAAGGTTTGA

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Fig. 12(A)

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      9      18      27      36      45      54
5' ATG GGA TGG AGC TGT ATC ATC CTC TTC TTG GTA GCA ACA GCT ACA GGT GTC CAC
   M  G  W  S  C  I  I  L  F  L  V  A  T  A  T  G  V  H
-----
      63      72      81      90      99      108
TCC CAG GTG CAG CTG GTG CAG TCT GGG GCA GAG GTG AAA AAG CCT GGG GCC TCA
   S  Q  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  A  S
-----
      117      126      135      144      153      162
GTG AAG GTG TCC TGC AAG GCT TCT GGC TAC ACC TTC AGT GCC TAC TGG ATA GAG
   V  K  V  S  C  K  A  S  G  Y  T  F  S  A  Y  W  I  E
-----
      171      180      189      198      207      216
TGG GTG CGC CAG GCT CCA GGA AAG GGC CTC GAG TGG GTC GGA GAG ATT TTA CCT
   W  V  R  Q  A  P  G  K  G  L  E  W  V  G  E  I  L  P
-----
      225      234      243      252      261      270
GGA AGT AAT AAT TCT AGA TAC AAT GAG AAG TTC AAG GGC CGA GTG ACA GTC ACT
   G  S  N  N  S  R  Y  N  E  K  F  K  G  R  V  T  V  T
-----
      279      288      297      306      315      324
AGA GAC ACA TCC ACA AAC ACA GCC TAC ATG GAG CTC AGC AGC CTG AGG TCT GAG
   R  D  T  S  T  N  T  A  Y  M  E  L  S  S  L  R  S  E
-----
      333      342      351      360      369      378
GAC ACA GCC GTC TAT TAC TGT GCA AGA TCC TAC GAC TTT GCC TGG TTT GCT TAC
   D  T  A  V  Y  Y  C  A  R  S  Y  D  F  A  W  F  A  Y
-----
      387      396      405      414      423      432
TGG GGC CAA GGG ACT CTG GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG
   W  G  Q  G  T  L  V  T  V  S  S  A  S  T  K  G  P  S
-----
      441      450      459      468      477      486
GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC CTG
   V  F  P  L  A  P  S  S  K  S  T  S  G  G  T  A  A  L
-----
      495      504      513      522      531      540
GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA
   G  C  L  V  K  D  Y  F  P  E  P  V  T  V  S  W  N  S
-----
      549      558      567      576      585      594
GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA
   G  A  L  T  S  G  V  H  T  F  P  A  V  L  Q  S  S  G
-----
      603      612      621      630      639      648
CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG
   L  Y  S  L  S  S  V  V  T  V  P  S  S  S  L  G  T  Q
-----
      657      666      675      684      693      702

```

Fig. 12(B)
(Sheet 1 of 4)

			9			18			27			36			45			54
5	ATG	GGA	TGG	AGC	TGT	ATC	ATC	CTC	TTC	TTC	GTA	GCA	ACA	GCT	ACA	GGT	GTC	CAC
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	M	G	W	S	C	I	I	L	F	L	V	A	T	A	T	G	V	H
			63			72			81			90			99			108
	TCC	CAG	GTG	CAG	CTG	GTG	CAG	TCT	GGG	GCA	GAG	GTG	AAA	AAG	CCT	GGG	GCC	TCA
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	S	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S
			117			126			135			144			153			162
	GTG	AAG	GTG	TCC	TGC	AAG	GCT	TCT	GGC	TAC	ACC	TTC	AGT	GCC	TAC	TGG	ATA	GAG
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	V	K	V	S	C	K	A	S	G	Y	T	F	S	A	Y	W	I	E
			171			180			189			198			207			216
	TGG	GTG	CGC	CAG	GCT	CCA	GGA	AAG	GGC	CTC	GAG	TGG	GTC	GGA	GAG	ATT	TTA	CCT
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	W	V	R	Q	A	P	G	K	G	L	E	W	V	G	E	I	L	P
			225			234			243			252			261			270
	GGA	AGT	AAT	AAT	TCT	AGA	TAC	AAT	GAG	AAG	TTC	AAG	GGC	CGA	GTG	ACA	GTC	ACT
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	G	S	N	N	S	R	Y	N	E	K	F	K	G	R	V	T	V	T
			279			288			297			306			315			324
	AGA	GAC	ACA	TCC	ACA	AAC	ACA	GCC	TAC	ATG	GAG	CTC	AGC	AGC	CTG	AGG	TCT	GAG
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	R	D	T	S	T	N	T	A	Y	M	E	L	S	S	L	R	S	E
			333			342			351			360			369			378
	GAC	ACA	GCC	GTC	TAT	TAC	TGT	GCA	AGA	TCC	TAC	GAC	TTT	GCC	TGG	TTT	GCT	TAC
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	D	T	A	V	Y	Y	C	A	R	S	Y	D	F	A	W	F	A	Y
			387			396			405			414			423			432
	TGG	GGC	CAA	GGG	ACT	CTG	GTC	ACA	GTC	TCC	TCA	GCC	TCC	ACC	AAG	GGC	CCA	TCG
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	W	G	Q	G	T	L	V	T	V	S	S	A	S	T	K	G	P	S
			441			450			459			468			477			486
	GTC	TTC	CCC	CTG	GCA	CCC	TCC	TCC	AAG	AGC	ACC	TCT	GGG	GGC	ACA	GCG	GCC	CTG
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	V	F	P	L	A	P	S	S	K	S	T	S	G	G	T	A	A	L
			495			504			513			522			531			540
	GGC	TGC	CTG	GTC	AAG	GAC	TAC	TTC	CCC	GAA	CCG	GTG	ACG	GTG	TCG	TGG	AAC	

Fig. 12(B)
(Sheet 1 of 4)

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ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA
---
T Y I C N V N H K P S N T K V D K K

711 720 729 738 747 756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG TGC CCA GCA CCT
---
V E P K S C D K T H T C P P C P A P

765 774 783 792 801 810
GAA CTC CTG GGG GGA CCG TCA GTC TTC CTC TTC CCC CCA AAA CCC AAG GAC ACC
---
E L L G G P S V F L F P P K P K D T

819 828 837 846 855 864
CTC ATG ATC TCC CGG ACC CCT GAG GTC ACA TGC GTG GTG GTG GAC GTG AGC CAC
---
L M I S R T P E V T C V V V D V S H

873 882 891 900 909 918
GAA GAC CCT GAG GTC AAG TTC AAC TGG TAC GTG GAC GGC GTG GAG GTG CAT AAT
---
E D P E V K F N W Y V D G V E V H N

927 936 945 954 963 972
GCC AAG ACA AAG CCG CGG GAG GAG CAG TAC AAC AGC ACG TAC CGT GTG GTC AGC
---
A K T K P R E E Q Y N S T Y R V V S

981 990 999 1008 1017 1026
GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAT GGC AAG GAG TAC AAG TGC AAG
---
V L T V L H Q D W L N G K E Y K C K

1035 1044 1053 1062 1071 1080
GTC TCC AAC AAA GCC CTC CCA GCC CCC ATC GAG AAA ACC ATC TCC AAA GCC AAA
---
V S N K A L P A P I E K T I S K A K

1089 1098 1107 1116 1125 1134
GGG CAG CCC CGA GAA CCA CAG GTG TAC ACC CTG CCC CCA TCC CGG GAT GAG CTG
---
G Q P R E P Q V Y T L P P S R D E L

1143 1152 1161 1170 1179 1188
ACC AAG AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAT CCC AGC GAC
---
T K N Q V S L T C L V K G F Y P S D

1197 1206 1215 1224 1233 1242
ATC GCC GTG GAG TGG GAG AGC AAT GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG
---
I A V E W E S N G Q P E N N Y K T T

1251 1260 1269 1278 1287 1296
CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC AAG CTC ACC GTG
---
P P V L D S D G S F F L Y S K L T V

1305 1314 1323 1332 1341 1350
GAC AAG AGC AGG TGG CAG CAG GGG AAC GTC TTC TCA TGC TCC GTG ATG CAT GAG
---
D K S R W Q Q G N V F S C S V M H E

```

Fig. 12(B)
(Sheet 2 of 4)

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1359	1368	1377	1386	1395	1404
GCT CTG CAC AAC CAC TAC ACG CAG AAG AGC CTC TCC CTG TCC CCG GGG AGC GGC					
A L H N H Y T Q K S L S L S P <u>G S G</u>					
1413	1422	1431	1440	1449	1458
GGG CTG AAG ATC GCA GCC TTC AAC ATC CAG ACA TTT GGG GAG ACC AAG ATG TCC					
<u>G</u> L K I A A F N I Q T F G E T K M S					
1467	1476	1485	1494	1503	1512
AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG ATC CTG AGC CGC TAC GAC ATC GCC					
N A T L V S Y I V Q I L S R Y D I A					
1521	1530	1539	1548	1557	1566
CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG ACT GCC GTG GGG AAG CTG CTG GAC					
L V Q E V R D S H L T A V G K L L D					
1575	1584	1593	1602	1611	1620
AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT CAC TAC GTG GTC AGT GAG CCA CTG					
N L N Q D A P D T Y H Y V V S E P L					
1629	1638	1647	1656	1665	1674
GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG TTC GTG TAC AGG CCT GAC CAG GTG					
G R N S Y K E R Y L F V Y R P D Q V					
1683	1692	1701	1710	1719	1728
TCT GCG GTG GAC AGC TAC TAC TAC GAT GAT GGC TGC GAG CCC TGC GGG AAC GAC					
S A V D S Y Y Y D D G C E P C G N D					
1737	1746	1755	1764	1773	1782
ACC TTC AAC CGA GAG CCA GCC ATT GTC AGG TTC TTC TCC CGG TTC ACA GAG GTC					
T F N R E P A I V R F F S R F T E V					
1791	1800	1809	1818	1827	1836
AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG GCC CCG GGG GAG GCA GTA GCC GAG					
R E F A I V P L H A A P G D A V A E					
1845	1854	1863	1872	1881	1890
ATC GAC GCT CTC TAT GAC GTC TAC CTG GAT GTC CAA GAG AAA TGG GGC TTG GAG					
I D A L Y D V Y L D V Q E K W G L E					
1899	1908	1917	1926	1935	1944
GAC GTC ATG TTG ATG GGC GAC TTC AAT GCG GGC TGC AGC TAT GTG AGA CCC TCC					
D V M L M G D F N A G C S Y V R P S					
1953	1962	1971	1980	1989	1998
CAG TGG TCA TCC ATC CGC CTG TGG ACA AGC CCC ACC TTC CAG TGG CTG ATC CCC					
Q W S S I R L W T S P T F Q W L I P					
2007	2016	2025	2034	2043	2052
GAC AGC GCT GAC ACC ACA GCT ACA CCC ACG CAC TGT GCC TAT GAC AGG ATC GTG					
D S A D T T A T P T H C A Y D R I V					

*Fig. 12(B)**(Sheet 3 of 4)*

SUBSTITUTE SHEET (RULE 26)

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2061	2070	2079	2088	2097	2106
GTT GCA GGG ATG CTG CTC CGA GGG GCC GTT GTT CCC GAC TCG GCT CTT CCC TTT					
V A G M L L R G A V V P D S A L P F					
2115	2124	2133	2142	2151	2160
AAC TTC CAG GCT GCC TAT GGC CTG AGT GAC CAA CTG GCC CAA GCC ATC AGT GAC					
N F Q A A Y G L S D Q L A Q A I S D					
2169	2178	2187	2196	2205	2214
CAC TAT CCA GTG GAG GTG ATG CTG AAG GGG GGC GGA CCC AAA AAG AAG CGC AAG					
H Y P V E V M L K G G G P K K K R K					

GTT TGA 3'

V

Fig. 12(B)
(Sheet 4 of 4)

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pAS101

LOCUS PAS101.DNA 1548 bp mRNA PRI 06-MAR-1995
 DEFINITION Humanised HMFG1 Fab'2 fused to human DNase I (pAS101)
 ACCESSION
 NID
 KEYWORDS DNase I.
 SOURCE DNase I sequence is from assembled oligos (thus modified c/f
 MHDNASE1.dna)
 ORGANISM Homo sapiens
 Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
 Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
 AUTHORS Shak,S., Capon,D.J., Hellmiss,R., Marsters,S.A. and Baker,C.L.
 TITLE Recombinant human DNase I reduces the viscosity of cystic
 fibrosis
 sputum
 JOURNAL Proc. Natl. Acad. Sci. U.S.A. 87 (23), 9188-9192 (1990)
 MEDLINE 91067672
 BASE COUNT 343 a 467 c 430 g 308 t
 ORIGIN

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1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCAGTGCC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTIONC CCCGAACCGG TGACGGTGTG GTGGAACCTA
541 GCGGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCTCT AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAAACCT ACACATGCCC ACCGTGCCCA GCACCTGAAG GCGGGCTGAA GATCGCAGCC
781 TTCAACATCC AGACATTGCG GGAGACCAAG ATGTCCAATG CCACCCTCGT CAGCTACATT
841 GTGCAGATCC TGAGCCGCTA CGACATCGCC CTGGTCCAGG AGGTCAGAGA CAGCCACCTG
901 ACTGCCGTGG GGAAGCTGCT GGACAACCTC AATCAGGACG CACCAGACAC CTATCACTAC
961 GTGGTCAGTG AGCCACTGGG ACGGAACAGC TATAAGGAGC GCTACCTGTT CGTGTACAGG
1021 CCTGACCAGG TGTCTGCGGT GGACAGCTAC TACTACGATG ATGGCTGCCA GCCCTGCGGG
1081 AACGACACCT TCAACCGAGA GCCAGCCATT GTCAGGTTCT TCTCCCGGTT CACAGAGGTC
1141 AGGGAGTTTG CCATTGTTC CCTGCATGCG GCGCCGGGGG ACGCAGTAGC CGAGATCGAC
1201 GCTCTCTATG ACGTCTACCT GGATGTCCAA GAGAAATGGG GCTTGGAGGA CGTCATGTTG
1261 ATGGGCGACT TCAATGCGGG CTGCAGCTAT GTGAGACCCT CCCAGTGGTC ATCCATCCGC
1321 CTGTGGACAA GCGCCACCTT CCAGTGGCTG ATCCCCGACA GCGCTGACAC CACAGCTACA
1381 CCCACGCACT GTGCCTATGA CAGGATCGTG GTTGCAGGGA TGCTGCTCCG AGGGGCCGTT
1441 GTTCCCGACT CGGCTCTTCC CTTTAACTTC CAGGCTGCCT ATGGCCTGAG TGACCAACTG
1501 GCGCAAGCCA TCAGTGACCA CTATCCAGTG GAGGTGATGC TGAAGTGA

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Fig. 13(A)

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LOCUS FDDNASE101 1548 BP SS-DNA SYN 25-AUG-2000
 DEFINITION -
 ACCESSION -
 KEYWORDS -
 SOURCE -
 FEATURES
 Location/Qualifiers
 frag join(1..>720,<781..1548)
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 frag 721..780
 /note="1 to 60 of 101/105linker"
 frag join(721..>735,<736..>759,<760..>780)
 /note="1 to 80 of 102linker [Split]"
 BASE COUNT 343 A 465 C 431 G 309 T 0 OTHER
 ORIGIN -
 1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
 61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
 121 TGCAAGGCTT CTGGCTACAC CTTCAGTGCC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
 181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
 241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
 301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
 361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
 421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
 481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAACCTCA
 541 GGCGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC
 601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
 661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
 721 GACAAACTC ACACATGTCC ACCGTGTCCA GCACCAGAGG GCGGGCTGAA GATCGCAGCC
 781 TTCAACATCC AGACATTTGG GGAGACCAAG ATGTCCAATG CCACCCTCGT CAGCTACATT
 841 GTGCAGATCC TGAGCCGCTA CGACATCGCC CTGGTCCAGG AGGTCAGAGA CAGCCACCTG
 901 ACTGCCGTGG GGAAGCTGCT GGACAACCTC AATCAGGACG CACCAGACAC CTATCACTAC
 961 GTGGTCAGTG AGCCACTGGG ACGGAACAGC TATAAGGAGC GCTACCTGTT CGTGTACAGG
 1021 CCTGACCAGG TGTCTGCGGT GGACAGCTAC TACTACGATG ATGGCTGCCA GCCCTGCCGG
 1081 AACGACACCT TCAACCGAGA GCCAGCCATT GTCAGGTTCT TCTCCCGGTT CACAGAGGTC
 1141 AGGGAGTTTG CCATTGTTCC CCTGCATGCG GCCCGGGGGG ACGCAGTAGC CGAGATCGAC
 1201 GCTCTCTATG ACGTCTACCT GGATGTCCAA GAGAAATGGG GCTTGGAGGA CGTCATGTTG
 1261 ATGGGCGACT TCAATGCGGG CTGCAGCTAT GTGAGACCCT CCCAGTGATC ATCCATCCGC
 1321 CTGTGGACAA GCCCCACCTT CCAGTGGCTG ATCCCCGACA GCGCTGACAC CACAGCTACA
 1381 CCCACGCACT GTGCCTATGA CAGGATCGTG GTTGCAGGGA TGCTGCTCCG AGGGGCCGTT
 1441 GTTCCCGACT CGGCTCTTCC CTTTAACTTC CAGGCTGCCT ATGGCCTGAG TGACCAACTG
 1501 GCCCAAGCCA TCAGTGACCA CTATCCAGTG GAGGTGATGC TGAAGTGA

Fig. 13(B)

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LOCUS FDDNASE101 1557 BP SS-DNA SYN 29-AUG-2000
 DEFINITION -
 ACCESSION -
 KEYWORDS -
 SOURCE -
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 Location/Qualifiers
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 /note="1 to 1548 of PAS101.dna [Split]"
 frag 730..789
 /note="1 to 60 of 101/105linker"
 frag join(730..>744,<745..>768,<769..>789)
 /note="1 to 80 of 102linker [Split]"
 BASE COUNT 344 A 471 C 433 G 309 T 0 OTHER
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 61 CACTCCCAGG TGCAGCTGGT GCAGTCTGGG GCAGAGGTGA AAAAGCCTGG GGCCTCAGTG
 121 AAGGTGTCCT GCAAGGCTTC TGGCTACACC TTCAGTGCCT ACTGGATAGA GTGGGTGCGC
 181 CAGGCTCCAG GAAAGGGCCT CGAGTGGGTC GGAGAGATTT TACCTGGAAG TAATAATTCT
 241 AGATACAATG AGAAGTTCAA GGGCCGAGTG ACAGTCACTA GAGACACATC CACAAACACA
 301 GCCTACATGG AGCTCAGCAG CCTGAGGTCT GAGGACACAG CCGTCTATTA CTGTGCAAGA
 361 TCCTACGACT TTGCCTGGTT TGCTTACTGG GGCCAGGGA CTCTGGTCAC AGTCTCCTCA
 421 GCCTCCACCA AGGGCCCATC GGTCTTCCCC CTGGCACCTT CCTCCAAGAG CACCTCTGGG
 481 GGCACAGCGG CCCTGGGCTG CCTGGTCAAG GACTACTTCC CCGAACCGGT GACGGTGTCG
 541 TGGAATCAG GCGCCCTGAC CAGCGGCGTG CACACCTTCC CGGCTGTCTT ACAGTCTCTCA
 601 GGACTCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAGCTTGGG CACCCAGACC
 661 TACATCTGCA ACGTGAATCA CAAGCCCAGC AACACCAAGG TGGACAAGAA AGTTGAGCCC
 721 AAATCTTGTG ACAAACCTCA CACATGTCCA CCGTGTCCAG CACCAGAGGG CGGGCTGAAG
 781 ATCGCAGCCT TCAACATCCA GACATTTGGG GAGACCAAGA TGTCCAATGC CACCTCGTTC
 841 AGCTACATTG TGCAGATCCT GAGCCGCTAC GACATCGCCC TGGTCCAGGA GGTGAGAGAC
 901 AGCCACCTGA CTGCCGTGGG GAAGCTGCTG GACAACCTCA ATCAGGACGC ACCAGACACC
 961 TATCACTACG TGGTCAGTGA GCCACTGGGA CGGAACAGCT ATAAGGAGCG CTACCTGTTC
 1021 GTGTACAGGC CTGACCAGGT GTCTGCGGTG GACAGCTACT ACTACGATGA TGGCTGCGAG
 1081 CCCTGCGGGA ACGACACCTT CAACCGAGAG CCAGCCATTG TCAGGTTCTT CTCCCGGTTT
 1141 ACAGAGGTCA GGGAGTTTGC CATTGTTCCC CTGCATGCGG CCCCAGGGGA CGCAGTAGCC
 1201 GAGATCGACG CTCTCTATGA CGTCTACCTG GATGTCCAAG AGAAATGGGG CTTGGAGGAC
 1261 GTCATGTTGA TGGGCGACTT CAATGCGGGC TGCAGCTATG TGAGACCCCTC CCAGTGGTCA
 1321 TCCATCCGCC TGTGGACAAG CCCCACCTTC CAGTGGCTGA TCCCCGACAG CGCTGACACC
 1381 ACAGCTACAC CCACGCACTG TGCCTATGAC AGGATCGTGG TTGCAAGGAT GCTGCTCCGA
 1441 GGGGCCGTTG TTCCCGACTC GGCTCTTCCC TTTAACTTCC AGGCTGCCTA TGGCCTGAGT
 1501 GACCAACTGG CCAAGCCAT CAGTGACCAC TATCCAGTGG AGGTGATGCT GAAAGTGA

//

Fig. 13(C)

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```

      9      18      27      36      45      54
5' ATG GGA TGG AGC TGT ATC ATC CTC TTC TTG GTA GCA ACA GCT ACA GGT GTC CAC
   -----
   M  G  W  S  C  I  I  L  F  L  V  A  T  A  T  G  V  H

      63      72      81      90      99      108
TCC CAG GTG CAG CTG GTG CAG TCT GGG GCA GAG GTG AAA AAG CCT GGG GCC TCA
   -----
   S  Q  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  A  S

      117      126      135      144      153      162
GTG AAG GTG TCC TGC AAG GCT TCT GGC TAC ACC TTC AGT GCC TAC TGG ATA GAG
   -----
   V  K  V  S  C  K  A  S  G  Y  T  F  S  A  Y  W  I  E

      171      180      189      198      207      216
TGG GTG CGC CAG GCT CCA GGA AAG GGC CTC GAG TGG GTC GGA GAG ATT TTA CCT
   -----
   W  V  R  Q  A  P  G  K  G  L  E  W  V  G  E  I  L  P

      225      234      243      252      261      270
GGA AGT AAT AAT TCT AGA TAC AAT GAG AAG TTC AAG GGC CGA GTG ACA GTC ACT
   -----
   G  S  N  N  S  R  Y  N  E  K  F  K  G  R  V  T  V  T

      279      288      297      306      315      324
AGA GAC ACA TCC ACA AAC ACA GCC TAC ATG GAG CTC AGC AGC CTG AGG TCT GAG
   -----
   R  D  T  S  T  N  T  A  Y  M  E  L  S  S  L  R  S  E

      333      342      351      360      369      378
GAC ACA GCC GTC TAT TAC TGT GCA AGA TCC TAC GAC TTT GCC TGG TTT GCT TAC
   -----
   D  T  A  V  Y  Y  C  A  R  S  Y  D  F  A  W  F  A  Y

      387      396      405      414      423      432
TGG GGC CAA GGG ACT CTG GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG
   -----
   W  G  Q  G  T  L  V  T  V  S  S  A  S  T  K  G  P  S

      441      450      459      468      477      486
GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC CTG
   -----
   V  F  P  L  A  P  S  S  K  S  T  S  G  G  T  A  A  L

      495      504      513      522      531      540
GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA
   -----
   G  C  L  V  K  D  Y  F  P  E  P  V  T  V  S  W  N  S

      549      558      567      576      585      594
GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA
   -----
   G  A  L  T  S  G  V  H  T  F  P  A  V  L  Q  S  S  G

```

Fig. 13(D)
(Sheet 1 of 3)

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603	612	621	630	639	648
CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG					
---	---	---	---	---	---
L Y S L S S V V T V P S S S L G T Q					
657	666	675	684	693	702
ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA					
---	---	---	---	---	---
T Y I C N V N H K P S N T K V D K K					
711	720	729	738	747	756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG TGC CCA GCA CCT					
---	---	---	---	---	---
V E P K S C D K T H T C P P C P A P					
765	774	783	792	801	810
GAA GGC GGG CTG AAG ATC GCA GCC TTC AAC ATC CAG ACA TTT GGG GAG ACC AAG					
---	---	---	---	---	---
E G G L K I A A F N I Q T F G E T K					
819	828	837	846	855	864
ATG TCC AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG ATC CTG AGC CGC TAC GAC					
---	---	---	---	---	---
M S N A T L V S Y I V Q I L S R Y D					
873	882	891	900	909	918
ATC GCC CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG ACT GCC GTG GGG AAG CTG					
---	---	---	---	---	---
I A L V Q E V R D S H L T A V G K L					
927	936	945	954	963	972
CTG GAC AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT CAC TAC GTG GTC AGT GAG					
---	---	---	---	---	---
L D N L N Q D A P D T Y H Y V V S E					
981	990	999	1008	1017	1026
CCA CTG GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG TTC GTG TAC AGG CCT GAC					
---	---	---	---	---	---
P L G R N S Y K E R Y L F V Y R P D					
1035	1044	1053	1062	1071	1080
CAG GTG TCT GCG GTG GAC AGC TAC TAC TAC GAT GAT GGC TGC GAG CCC TGC GGG					
---	---	---	---	---	---
Q V S A V D S Y Y Y D D G C E P C G					
1089	1098	1107	1116	1125	1134
AAC GAC ACC TTC AAC CGA GAG CCA GCC ATT GTC AGG TTC TTC TCC CGG TTC ACA					
---	---	---	---	---	---
N D T F N R E P A I V R F F S R F T					
1143	1152	1161	1170	1179	1188
GAG GTC AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG GCC CCG GGG GAC GCA GTA					
---	---	---	---	---	---
E V R E F A I V P L H A A P G D A V					
1197	1206	1215	1224	1233	1242

Fig. 13(D)
(Sheet 2 of 3)

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GCC GAG ATC GAC GCT CTC TAT GAC GTC TAC CTG GAT GTC CAA GAG AAA TGG GGC
---
A E I D A L Y D V Y L D V Q E K W G

      1251      1260      1269      1278      1287      1296
TTG GAG GAC GTC ATG TTG ATG GGC GAC TTC AAT GCG GGC TGC AGC TAT GTG AGA
---
L E D V M L M G D F N A G C S Y V R

      1305      1314      1323      1332      1341      1350
CCC TCC CAG TGG TCA TCC ATC CGC CTG TGG ACA AGC CCC ACC TTC CAG TGG CTG
---
P S Q W S S I R L W T S P T F Q W L

      1359      1368      1377      1386      1395      1404
ATC CCC GAC AGC GCT GAC ACC ACA GCT ACA CCC ACG CAC TGT GCC TAT GAC AGG
---
I P D S A D T T A T P T H C A Y D R

      1413      1422      1431      1440      1449      1458
ATC GTG GTT GCA GGG ATG CTG CTC CGA GGG GCC GTT GTT CCC GAC TCG GCT CTT
---
I V V A G M L L R G A V V P D S A L

      1467      1476      1485      1494      1503      1512
CCC TTT AAC TTC CAG GCT GCC TAT GGC CTG AGT GAC CAA CTG GCC CAA GCC ATC
---
P F N F Q A A Y G L S D Q L A Q A I

      1521      1530      1539      1548
AGT GAC CAC TAT CCA GTG GAG GTG ATG CTG AAG TGA 3'
---
S D H Y P V E V M L K *
```

Fig. 13(D)
(Sheet 3 of 3)

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pAS102

LOCUS PAS102.DNA 1566 bp mRNA PRI 06-MAR-1995
 DEFINITION Humanised HMFG1 Fab'2 fused to human DNase I (pAS102)
 ACCESSION
 NID
 KEYWORDS DNase I.
 SOURCE DNase I sequence is from assembled oligos (thus modified c/f
 MHDNASE1.dna) (See Figure 2)
 ORGANISM Homo sapiens
 Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
 Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
 AUTHORS Shak, S., Capon, D.J., Hellmiss, R., Marsters, S.A. and Baker, C.L.
 TITLE Recombinant human DNase I reduces the viscosity of cystic
 fibrosis
 sputum
 JOURNAL Proc. Natl. Acad. Sci. U.S.A. 87 (23), 9188-9192 (1990)
 MEDLINE 91067672
 BASE COUNT 345 a 469 c 440 g 312 t
 ORIGIN

```

1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCACTGCC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTIONC CCCGAACCGG TGACGGTGTG GTGGAACCTCA
541 GCGGCCCTGA CCAGCGGCGT GCACACCTTC CCGCTGTCC TACAGTCTC AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAAATC ACACATGCTG TGTGGAGTGC CCACCGTGCC CAGCACCTGA AGGGAGCGGC
781 GGGCTGAAGA TCGCAGCCTT CAACATCCAG ACATTTGGGG AGACCAAGAT GTCCAATGCC
841 ACCCTCGTCA GCTACATTGT GCAGATCCTG AGCCGCTACG ACATCGCCCT GGTCCAGGAG
901 GTCAGAGACA GCCACCTGAC TGCCGTGGGG AAGCTGCTGG ACAACCTCAA TCAGGACGCA
961 CCAGACACCT ATCACTACGT GGTCACTGAG CCACTGGGAC GGAACAGCTA TAAGGAGCGC
1021 TACCTGTTCC TGTACAGGCC TGACCAGGTG TCTGCGGTGG ACAGCTACTA CTACGATGAT
1081 GGCTGCGAGC CCTGCGGGAA CGACACCTTC AACCGAGAGC CAGCCATTGT CAGGTTCTTC
1141 TCCCGGTTCA CAGAGGTCAG GGAGTTTGCC ATTGTTCCCC TGCATGCGGC CCCGGGGGAC
1201 GCAGTAGCCG AGATCGACGC TCTCTATGAC GTCTACCTGG ATGTCCAAGA GAAATGGGGC
1261 TTGGAGGACG TCATGTTGAT GGGCGACTTC AATGCGGGCT GCAGCTATGT GAGACCCTCC
1321 CAGTGGTCAT CCATCCGCCT GTGGACAAGC CCCACCTTCC AGTGGCTGAT CCCCAGACAGC
1381 GCTGACACCA CAGCTACACC CACGCACTGT GCCTATGACA GGATCGTGGT TGCAGGGATG
1441 CTGCTCCGAG GGGCCGTTGT TCCCGACTCG GCTCTTCCTT TTAACCTCCA GGCTGCCTAT
1501 GGCTGAGTG ACCAAGTGGC CCAAGCCATC AGTGACCACT ATCCAGTGGA GGTGATGCTG
1561 AAGTGA

```

//

Fig. 14(A)

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LOCUS FDDNASE102 1566 BP SS-DNA SYN 23-MAR-2001
 DEFINITION -
 ACCESSION -
 KEYWORDS -
 SOURCE -
 BASE COUNT 345 A 468 C 440 G 313 T 0 OTHER
 ORIGIN -

```

1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCAAGTGC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCCTGG TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAAGTCA
541 GGCGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAACTC ACACATGCTG TGTCGAGTGT CCACCGTGTG CAGCACCAGA GGGGAGCGGC
781 GGGCTGAAGA TCGCAGCCTT CAACATCCAG ACATTGTTGGG AGACCAAGAT GTCCAATGCC
841 ACCCTCGTCA GCTACATTGT GCAGATCTTG AGCCGCTACG ACATCGCCCT GGTCCAGGAG
901 GTCAGAGACA GCCACCTGAC TGCCGTGGGG AAGCTGCTGG ACAACCTCAA TCAGGACGCA
961 CCAGACACCT ATCACTACGT GGTCAAGTGA CCACTGGGAC GGAACAGCTA TAAGGAGCGC
1021 TACCTGTTCTG TGTACAGGCC TGACCAGGTG TCTGCGGTGG ACAGCTACTA CTACGATGAT
1081 GGCTGCGAGC CCTGCGGGAA CGACACCTTC AACCAGAGAC CAGCCATTGT CAGGTTCTTC
1141 TCCCGGTTCA CAGAGGTCAG GGAGTTTGCC ATTGTTCCCC TGCATGCGGC CCCGGGGGAC
1201 GCAGTAGCCG AGATCGACGC TCTCTATGAC GTCTACCTGG ATGTCCAAGA GAAATGGGGC
1261 TTGGAGGACG TCATGTTGAT GGGCGACTTC AATGCGGGCT GCAGCTATGT GAGACCCTCC
1321 CAGTGGTCAT CCATCCGCCT GTGGACAAGC CCCACCTTCC AGTGGCTGAT CCCCAGACAGC
1381 GCTGACACCA CAGCTACACC CACGCACTGT GCCTATGACA GGATCGTGGT TGCAGGGATG
1441 CTGCTCCGAG GGGCCGTTGT TCCCAGACTCG GCTCTTCCCT TTAACCTCCA GGCTGCCTAT
1501 GGCCTGAGTG ACCAACTGGC CCAAGCCATC AGTGACCACT ATCCAGTGGA GGTGATGCTG
1561 AAGTGA

```

Fig. 14(B)

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pAS302

LOCUS FDDNASE302 1575 BP SS-DNA SYN 29-AUG-2000
 DEFINITION -
 ACCESSION -
 KEYWORDS -
 SOURCE -
 FEATURES Location/Qualifiers
 frag 10..1575
 /note="1 to 1566 of FdDNase102correct"
 BASE COUNT 346 A 474 C 442 G 313 T 0 OTHER
 ORIGIN -

```

1  GCGGCCACCA TGGGATGGAG CTGTATCATC CTCTTCTTGG TAGCAACAGC TACAGGTGTC
61  CACTCCCAGG TGCAGCTGGT GCAGTCTGGG GCAGAGGTGA AAAAGCCTGG GGCCTCAGTG
121 AAGGTGTCCT GCAAGGCTTC TGGCTACACC TTCAGTGCCT ACTGGATAGA GTGGGTGCGC
181 CAGGCTCCAG GAAAGGGCCT CGAGTGGGTC GGAGAGATT TACCTGGAAG TAATAATTCT
241 AGATACAATG AGAAGTTCAA GGGCCGAGTG ACAGTCACTA GAGACACATC CACAAACACA
301 GCCTACATGG AGCTCAGCAG CCTGAGGTCT GAGGACACAG CCGTCTATTA CTGTGCAAGA
361 TCCTACGACT TTGCCTGGTT TGCTTACTGG GGCCAAGGGA CTCTGGTCAC AGTCTCCTCA
421 GCCTCCACCA AGGGCCCATC GGTCTTCCCC CTGGCACCCCT CCTCCAAGAG CACCTCTGGG
481 GGCACAGCGG CCCTGGGCTG CCTGGTCAAG GACTACTTCC CCGAACCGGT GACGGTGTCTG
541 TGGAAGTCAG GCGCCCTGAC CAGCGGCGTG CACACCTTCC CGGCTGTCTT ACAGTCCTCA
601 GGAATCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAGCTTGGG CACCCAGACC
661 TACATCTGCA ACGTGAATCA CAAGCCCAGC AACACCAAGG TGGACAAGAA AGTTGAGCCC
721 AAATCTTGTC ACAAAGTCTA CACATGCTGT GTCGAGTGTG CACCGTGTCC AGCACCAGAG
781 GGGAGCGGCG GGCTGAAGAT CGCAGCCTTC AACATCCAGA CATTGTTGGGA GACCAAGATG
841 TCCAATGCCA CCCTCGTCAG CTACATTGTG CAGATCCTGA GCCGCTACGA CATCGCCCTG
901 GTCCAGGAGG TCAGAGACAG CCACCTGACT GCCGTGGGGA AGCTGCTGGA CAACCTCAAT
961 CAGGACGCAC CAGACACCTA TCACTACGTG GTCAGTGAGC CACTGGGACG GAACAGCTAT
1021 AAGGAGCGCT ACCTGTTTCT GTACAGGCCT GACCAGGTGT CTGCGGTGGA CAGCTACTAC
1081 TACGATGATG GCTGCGAGCC CTGCGGGAAC GACACCTTCA ACCGAGAGCC AGCCATTGTC
1141 AGGTCTTCTT CCCGGTTCAC AGAGGTCAGG GAGTTTGCCA TTGTTCCCTT GCATGCGGCC
1201 CCGGGGGACG CAGTAGCCGA GATCGACGCT CTCTATGACG TCTACCTGGA TGTTCAAGAG
1261 AAATGGGGCT TGGAGGACGT CATGTTGATG GGCGACTTCA ATGCGGGCTG CAGCTATGTG
1321 AGACCTCCC AGTGGTCATC CATCCGCTG TGGACAAGCC CCACCTTCCA GTGGCTGATC
1381 CCCGACAGCG CTGACACCAC AGCTACACCC ACGCACTGTG CCTATGACAG GATCGTGGTT
1441 GCAGGGATGC TGCTCCGAGG GGCCGTTGTT CCCGACTCGG CTCTTCCCTT TAACTTCCAG
1501 GCTGCCTATG GCCTGAGTGA CCAACTGGCC CAAGCCATCA GTGACCACTA TCCAGTGGAG
1561 GTGATGCTGA AGTGA

```

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Fig. 14(C)

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```

      9      18      27      36      45      54
5'  ATG GGA TGG AGC TGT ATC ATC CTC TTC TTG GTA GCA ACA GCT ACA GGT GTC CAC
    ---
      M  G  W  S  C  I  I  L  F  L  V  A  T  A  T  G  V  H

      63      72      81      90      99      108
TCC CAG GTG CAG CTG GTG CAG TCT GGG GCA GAG GTG AAA AAG CCT GGG GCC TCA
    ---
      S  Q  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  A  S

      117      126      135      144      153      162
GTG AAG GTG TCC TGC AAG GCT TCT GGC TAC ACC TTC AGT GCC TAC TGG ATA GAG
    ---
      V  K  V  S  C  K  A  S  G  Y  T  F  S  A  Y  W  I  E

      171      180      189      198      207      216
TGG GTG CGC CAG GCT CCA GGA AAG GGC CTC GAG TGG GTC GGA GAG ATT TTA CCT
    ---
      W  V  R  Q  A  P  G  K  G  L  E  W  V  G  E  I  L  P

      225      234      243      252      261      270
GGA AGT AAT AAT TCT AGA TAC AAT GAG AAG TTC AAG GGC CGA GTG ACA GTC ACT
    ---
      G  S  N  N  S  R  Y  N  E  K  F  K  G  R  V  T  V  T

      279      288      297      306      315      324
AGA GAC ACA TCC ACA AAC ACA GCC TAC ATG GAG CTC AGC AGC CTG AGG TCT GAG
    ---
      R  D  T  S  T  N  T  A  Y  M  E  L  S  S  L  R  S  E

      333      342      351      360      369      378
GAC ACA GCC GTC TAT TAC TGT GCA AGA TCC TAC GAC TTT GCC TGG TTT GCT TAC
    ---
      D  T  A  V  Y  Y  C  A  R  S  Y  D  F  A  W  F  A  Y

      387      396      405      414      423      432
TGG GGC CAA GGG ACT CTG GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG
    ---
      W  G  Q  G  T  L  V  T  V  S  S  A  S  T  K  G  P  S

      441      450      459      468      477      486
GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC CTG
    ---
      V  F  P  L  A  P  S  S  K  S  T  S  G  G  T  A  A  L

      495      504      513      522      531      540
GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA
    ---
      G  C  L  V  K  D  Y  F  P  E  P  V  T  V  S  W  N  S

      549      558      567      576      585      594
GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA
    ---
      G  A  L  T  S  G  V  H  T  F  P  A  V  L  Q  S  S  G

```

Fig. 14(D)
(Sheet 1 of 3)

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603	612	621	630	639	648
CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG					
L Y S L S S V V T V P S S S L G T Q					
657	666	675	684	693	702
ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA					
T Y I C N V N H K P S N T K V D K K					
711	720	729	738	747	756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC TGT GTG GAG TGC CCA CCC					
V E P K S C D K T H T C C V E C P P					
765	774	783	792	801	810
TGC CCA GCA CCT GAA GGG AGC GGC GGG CTG AAG ATC GCA GCC TTC AAC ATC CAG					
C P A P E G S G G L K I A A F N I Q					
819	828	837	846	855	864
ACA TTT GGG GAG ACC AAG ATG TCC AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG					
T F G E T K M S N A T L V S Y I V Q					
873	882	891	900	909	918
ATC CTG AGC CGC TAC GAC ATC GCC CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG					
I L S R Y D I A L V Q E V R D S H L					
927	936	945	954	963	972
ACT GCC GTG GGG AAG CTG CTG GAC AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT					
T A V G K L L D N L N Q D A P D T Y					
981	990	999	1008	1017	1026
CAC TAC GTG GTC AGT GAG CCA CTG GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG					
H Y V V S E P L G R N S Y K E R Y L					
1035	1044	1053	1062	1071	1080
TTC GTG TAC AGG CCT GAC CAG GTG TCT GCG GTG GAC AGC TAC TAC TAC GAT GAT					
F V Y R P D Q V S A V D S Y Y Y D D					
1089	1098	1107	1116	1125	1134
GGC TGC GAG CCC TGC GGG AAC GAC ACC TTC AAC CGA GAG CCA GCC ATT GTC AGG					
G C E P C G N D T F N R E P A I V R					
1143	1152	1161	1170	1179	1188
TTC TTC TCC CGG TTC ACA GAG GTC AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG					
F F S R F T E V R E F A I V P L H A					
1197	1206	1215	1224	1233	1242

Fig. 14(D)
(Sheet 2 of 3)

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GCC	CCG	GGG	GAC	GCA	GTA	GCC	GAG	ATC	GAC	GCT	CTC	TAT	GAC	GTC	TAC	CTG	GAT
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
A	P	G	D	A	V	A	E	I	D	A	L	Y	D	V	Y	L	D
		1251			1260			1269			1278			1287			1296
GTC	CAA	GAG	AAA	TGG	GGC	TTG	GAG	GAC	GTC	ATG	TTG	ATG	GGC	GAC	TTC	AAT	GCG
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
V	Q	E	K	W	G	L	E	D	V	M	L	M	G	D	F	N	A
		1305			1314			1323			1332			1341			1350
GGC	TGC	AGC	TAT	GTG	AGA	CCC	TCC	CAG	TGG	TCA	TCC	ATC	CGC	CTG	TGG	ACA	AGC
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
G	C	S	Y	V	R	P	S	Q	W	S	S	I	R	L	W	T	S
		1359			1368			1377			1386			1395			1404
CCC	ACC	TTC	CAG	TGG	CTG	ATC	CCC	GAC	AGC	GCT	GAC	ACC	ACA	GCT	ACA	CCC	ACG
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
P	T	F	Q	W	L	I	P	D	S	A	D	T	T	A	T	P	T
		1413			1422			1431			1440			1449			1458
CAC	TGT	GCC	TAT	GAC	AGG	ATC	GTG	GTT	GCA	GGG	ATG	CTG	CTC	CGA	GGG	GCC	GTT
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
H	C	A	Y	D	R	I	V	V	A	G	M	L	L	R	G	A	V
		1467			1476			1485			1494			1503			1512
GTT	CCC	GAC	TCG	GCT	CTT	CCC	TTT	AAC	TTC	CAG	GCT	GCC	TAT	GGC	CTG	AGT	GAC
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
V	P	D	S	A	L	P	F	N	F	Q	A	A	Y	G	L	S	D
		1521			1530			1539			1548			1557			1566
CAA	CTG	GCC	CAA	GCC	ATC	AGT	GAC	CAC	TAT	CCA	GTG	GAG	GTG	ATG	CTG	AAG	TGA
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Q	L	A	Q	A	I	S	D	H	Y	P	V	E	V	M	L	K	*

Fig. 14(D)
(Sheet 3 of 3)

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pAS103

LOCUS PAS103.DNA 1560 bp mRNA PRI 06-MAR-1995
 DEFINITION Humanised HMEG1 Fab'2 fused to human DNase I (pAS103)
 ACCESSION
 NID
 KEYWORDS DNase I.
 SOURCE DNase I sequence is from assembled oligos (thus modified c/f
 MHDNASE1.dna)
 ORGANISM Homo sapiens
 Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
 Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
 AUTHORS Shak,S., Capon,D.J., Hellmiss,R., Marsters,S.A. and Baker,C.L.
 TITLE Recombinant human DNase I reduces the viscosity of cystic
 fibrosis
 sputum
 JOURNAL Proc. Natl. Acad. Sci. U.S.A. 87 (23), 9188-9192 (1990)
 MEDLINE 91067672
 BASE COUNT 344 a 468 c 436 g 312 t
 ORIGIN

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1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCAGTGCC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAAC TCA
541 GGCGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAACTC ACACATGCTG TGTGGAGTGC CCACCGTGCC CAGCACCTGA AGGCGGGCTG
781 AAGATCGCAG CCTTCAACAT CCAGACATTT GGGGAGACCA AGATGTCCAA TGCCACCCTC
841 GTCAGCTACA TTGTGCAGAT CCTGAGCCGC TACGACATCG CCCTGGTCCA GGAGGTCAGA
901 GACAGCCACC TGACTGCCGT GGGGAAGCTG CTGGACAACC TCAATCAGGA CGCACCAGAC
961 ACCTATCACT ACGTGGTCAG TGAGCCACTG GGACGGAACA GCTATAAGGA GCGCTACCTG
1021 TTCGTGTACA GGCCTGACCA GGTGTCTGCG GTGGACAGCT ACTACTACGA TGATGGCTGC
1081 GAGCCCTGCG GGAACGACAC CTTCAACCGA GAGCCAGCCA TTGTCAGGTT CTTCTCCCGG
1141 TTCACAGAGG TCAGGGAGTT TGCCATTGTT CCCCTGCATG CGGCCCCGGG GGACGCAGTA
1201 GCCGAGATCG ACGCTCTCTA TGACGTCTAC CTGGATGTCC AAGAGAAATG GGGCTTGGAG
1261 GACGTCATGT TGATGGGCGA CTTCAATGCG GGCTGCAGCT ATGTGAGACC CTCCCAGTGG
1321 TCATCCATCC GCCTGTGGAC AAGCCCCACC TTCCAGTGGC TGATCCCCGA CAGCGCTGAC
1381 ACCACAGCTA CACCCACGCA CTGTGCCTAT GACAGGATCG TGGTTGCAGG GATGCTGCTC
1441 CGAGGGGCGG TTGTTCCCGA CTCGGCTCTT CCCTTTAACT TCCAGGCTGC CTATGGCCTG
1501 AGTGACCAAC TGGCCCAAGC CATCAGTGAC CACTATCCAG TGGAGGTGAT GCTGAAGTGA

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//

Fig. 15(A)

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LOCUS FDDNASE103 1560 BP SS-DNA SYN 25-AUG-2000

DEFINITION -

ACCESSION -

KEYWORDS -

SOURCE -

FEATURES

Location/Qualifiers

frag join(1..>720,<793..1560)

/note="1 to 1560 of PAS103.dna [Split]"

frag 721..792

/note="1 to 72 of 103/107linker"

frag join(721..>771,<772..792)

/note="1 to 78 of 102linker [Split]"

BASE COUNT 344 A 467 C 436 G 313 T 0 OTHER

ORIGIN

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61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC

121 TGCAAGGCTT CTGGCTACAC CTTCAAGTGC TACTGGATAG AGTGGGTGCG CCAGGCTCCA

181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT

241 GAGAAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG

301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC

361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC

421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG

481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAAC TCA

541 GGC GCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC

601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC

661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT

721 GACAAACTC ACACATGCTG TGTCGAGTGT CCACCGTGTG CAGCACCAGA GGGCGGGCTG

781 AAGATCGCAG CCTTCAACAT CCAGACATTT GGGGAGACCA AGATGTCCAA TGCCACCCTC

841 GTCAGCTACA TTGTGCAGAT CCTGAGCCGC TACGACATCG CCCTGGTCCA GGAGGTCAGA

901 GACAGCCACC TGA CTG CCGT GGGGAAGCTG CTGGACAACC TCAATCAGGA CGCACCAGAC

961 ACCTATCACT ACCTGGTCAG TGAGCCACTG GGACGGAACA GCTATAAGGA GCGCTACCTG

1021 TTCGTGTACA GGCTTGACCA GGTGTCTGCG GTGGACAGCT ACTACTACGA TGATGGCTGC

1081 GAGCCCTGCG GGAACGACAC CTTCAACCGA GAGCCAGCCA TTGTCAAGTT CTTCTCCCGG

1141 TTCACAGAGG TCAGGGAGTT TGCCATTGTT CCCCTGCATG CGGCCCGGGG GGACGCAGTA

1201 GCCGAGATCG ACGCTCTCTA TGACGTCTAC CTGGATGTCC AAGAGAAATG GGGCTTGGAG

1261 GACGTCATGT TGATGGGCGA CTTCAATGCG GGCTGCAGCT ATGTGAGACC CTCCCAGTGG

1321 TCATCCATCC GCCTGTGGAC AAGCCCCACC TTCCAGTGGC TGATCCCCGA CAGCGCTGAC

1381 ACCACAGCTA CACCCACGCA CTGTGCCTAT GACAGGATCG TGGTTGCAGG GATGCTGCTC

1441 CGAGGGGCGG TTGTTCCCGA CTCGGCTCTT CCCTTTAACT TCCAGGCTGC CTATGGCCTG

1501 AGTGACCAAC TGGCCCAAGC CATCAGTGAC CACTATCCAG TGGAGGTGAT GCTGAAGTGA

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Fig. 15(B)

66/113

LOCUS FDDNASE103 1569 BP SS-DNA SYN 29-AUG-2000
 DEFINITION -
 ACCESSION -
 KEYWORDS -
 SOURCE -
 FEATURES Location/Qualifiers
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 frag join(10..>729,<802..1569)
 /note="1 to 1560 of PAS103.dna [Split]"
 frag 730..801
 /note="1 to 72 of 103/107linker"
 frag join(730..>780,<781..801)
 /note="1 to 78 of 102linker [Split]"
 BASE COUNT 345 A 473 C 438 G 313 T 0 OTHER
 ORIGIN -
 1 GCGGCCACCA TGGGATGGAG CTGTATCATC CTCTTCTTGG TAGCAACAGC TACAGGTGTC
 61 CACTCCCAGG TGCAGCTGGT GCAGTCTGGG GCAGAGGTGA AAAAGCCTGG GGCCTCAGTG
 121 AAGGTGTCCT GCAAGGCTTC TGGCTACACC TTCAGTGCCT ACTGGATAGA GTGGGTGCGC
 181 CAGGCTCCAG GAAAGGGCCT CGAGTGGGTC GGAGAGATT TACCTGGAAG TAATAATTCT
 241 AGATACAATG AGAAGTTCAA GGGCCGAGTG ACAGTCACTA GAGACACATC CACAAACACA
 301 GCCTACATGG AGCTCAGCAG CCTGAGGTCT GAGGACACAG CCGTCTATTA CTGTGCAAGA
 361 TCCTACGACT TTGCCTGGTT TGCTTACTGG GGCCAAGGGA CTCTGGTCAC AGTCTCCTCA
 421 GCCTCCACCA AGGGCCCATC GGTCTTCCCC CTGGCACCCCT CCTCCAAGAG CACCTCTGGG
 481 GGCACAGCGG CCCTGGGCTG CCTGGTCAAG GACTACTTCC CCGAACCGGT GACGGTGTCG
 541 TGGAATCAG GCGCCCTGAC CAGCGGCGTG CACACCTTCC CGGCTGTCCT ACAGTCCTCA
 601 GGAATCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAGCTTGGG CACCCAGACC
 661 TACATCTGCA ACGTGAATCA CAAGCCCAGC AACACCAAGG TGGACAAGAA AGTTGAGCCC
 721 AAATCTTGTG ACAAACCTCA CACATGCTGT GTGAGGTGTC CACCGTGTCC AGCACCAGAG
 781 GGCGGGCTGA AGATCGCAGC CTTCAACATC CAGACATTTG GGGAGACCAA GATGTCCAAT
 841 GCCACCCTCG TCAGCTACAT TGTGCAGATC CTGAGCCGCT ACGACATCGC CCTGGTCCAG
 901 GAGGTCAGAG ACAGCCACCT GACTGCCGTG GGAAGCTGC TGGACAACCT CAATCAGGAC
 961 GCACCAGACA CCTATCACTA CGTGGTCAGT GAGCCACTGG GACGGAACAG CTATAAGGAG
 1021 CGCTACCTGT TCGTGTACAG GCCTGACCAG GTGTCTGCGG TGGACAGCTA CTACTACGAT
 1081 GATGGCTGCG AGCCCTGCGG GAACGACACC TTCAACCGAG AGCCAGCCAT TGTCAGGTTC
 1141 TTCTCCCGGT TCACAGAGGT CAGGGAGTTT GCCATTGTTT CCCTGCATGC GGCCCCGGGG
 1201 GACGCAGTAG CCGAGATCGA CGCTCTCTAT GACGTCTACC TGGATGTCCA AGAGAAATGG
 1261 GGCTTGAGAG ACGTCATGTT GATGGGCGAC TTCAATGCCG GCTGCAGCTA TGTGAGACCC
 1321 TCCAGTGGT CATCCATCCG CCTGTGGACA AGCCCCACCT TCCAGTGGCT GATCCCCGAC
 1381 AGCGCTGACA CCACAGCTAC ACCACGCGAC TGTGCCTATG ACAGGATCGT GGTTCAGGGG
 1441 ATGCTGCTCC GAGGGGCCGT TGTTCGGCAG TCGGCTCTTC CCTTTAACTT CCAGGCTGCC
 1501 TATGGCCTGA GTGACCAACT GGCCCAAGCC ATCAGTGACC ACTATCCAGT GGAGGTGATG
 1561 CTGAAGTGA

//

Fig. 15(C)

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```

          9      18      27      36      45      54
5' ATG GGA TGG AGC TGT ATC ATC CTC TTC TTG GTA GCA ACA GCT ACA GGT GTC CAC
---
M G W S C I I L F L V A T A T G V H

          63      72      81      90      99      108
TCC CAG GTG CAG CTG GTG CAG TCT GGG GCA GAG GTG AAA AAG CCT GGG GCC TCA
---
S Q V Q L V Q S G A E V K K P G A S

          117      126      135      144      153      162
GTG AAG GTG TCC TGC AAG GCT TCT GGC TAC ACC TTC AGT GCC TAC TGG ATA GAG
---
V K V S C K A S G Y T F S A Y W I E

          171      180      189      198      207      216
TGG GTG CGC CAG GCT CCA GGA AAG GGC CTC GAG TGG GTC GGA GAG ATT TTA CCT
---
W V R Q A P G K G L E W V G E I L P

          225      234      243      252      261      270
GGA AGT AAT AAT TCT AGA TAC AAT GAG AAG TTC AAG GGC CGA GTG ACA GTC ACT
---
G S N N S R Y N E K F K G R V T V T

          279      288      297      306      315      324
AGA GAC ACA TCC ACA AAC ACA GCC TAC ATG GAG CTC AGC AGC CTG AGG TCT GAG
---
R D T S T N T A Y M E L S S L R S E

          333      342      351      360      369      378
GAC ACA GCC GTC TAT TAC TGT GCA AGA TCC TAC GAC TTT GCC TGG TTT GCT TAC
---
D T A V Y Y C A R S Y D F A W F A Y

          387      396      405      414      423      432
TGG GGC CAA GGG ACT CTG GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG
---
W G Q G T L V T V S S A S T K G P S

          441      450      459      468      477      486
GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC CTG
---
V F P L A P S S K S T S G G T A A L

          495      504      513      522      531      540
GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA
---
G C L V K D Y F P E P V T V S W N S

          549      558      567      576      585      594
GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA
---
G A L T S G V H T F P A V L Q S S G

```

Fig. 15(D)
(Sheet 1 of 3)

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603	612	621	630	639	648
CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG					
---	---	---	---	---	---
L Y S L S S V V T V P S S S L G T Q					
657	666	675	684	693	702
ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA					
---	---	---	---	---	---
T Y I C N V N H K P S N T K V D K K					
711	720	729	738	747	756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC TGT GTG GAG TGC CCA CCG					
---	---	---	---	---	---
V E P K S C D K T H T C C V E C P P					
765	774	783	792	801	810
TGC CCA GCA CCT GAA GGC GGG CTG AAG ATC GCA GCC TTC AAC ATC CAG ACA TTT					
---	---	---	---	---	---
C P A P E G G L K I A A F N I Q T F					
819	828	837	846	855	864
GGG GAG ACC AAG ATG TCC AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG ATC CTG					
---	---	---	---	---	---
G E T K M S N A T L V S Y I V Q I L					
873	882	891	900	909	918
AGC CGC TAC GAC ATC GCC CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG ACT GCC					
---	---	---	---	---	---
S R Y D I A L V Q E V R D S H L T A					
927	936	945	954	963	972
GTG GGG AAG CTG CTG GAC AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT CAC TAC					
---	---	---	---	---	---
V G K L L D N L N Q D A P D T Y H Y					
981	990	999	1008	1017	1026
GTG GTC AGT GAG CCA CTG GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG TTC GTG					
---	---	---	---	---	---
V V S E P L G R N S Y K E R Y L F V					
1035	1044	1053	1062	1071	1080
TAC AGG CCT GAC GAG GAG TCT GCG GTG GAC AGC TAC TAC TAC GAT GAT GGC TGC					
---	---	---	---	---	---
Y R P D Q V S A V D S Y Y Y D D G C					
1089	1098	1107	1116	1125	1134
GAG CCC TGC GGG AAC GAC ACC TTC AAC CGA GAG CCA GCC ATT GTG AGG TTC TTC					
---	---	---	---	---	---
E P C G N D T F N R E P A I V R F F					
1143	1152	1161	1170	1179	1188
TCC CGG TTC ACA GAG GTC AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG GCC CCG					
---	---	---	---	---	---
S R F T E V R E F A I V P L H A A P					
1197	1206	1215	1224	1233	1242

Fig. 15(D)
(Sheet 2 of 3)

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```

GGG GAC GCA GTA GCC GAG ATC GAC GCT CTC TAT GAC GTC TAC CTG GAT GTC CAA
-----
G   D   A   V   A   E   I   D   A   L   Y   D   V   Y   L   D   V   Q

      1251      1260      1269      1278      1287      1296
GAG AAA TGG GGC TTG GAG GAC GTC ATG TTG ATG GGC GAC TTC AAT GCG GGC TGC
-----
E   K   W   G   L   E   D   V   M   L   M   G   D   F   N   A   G   C

      1305      1314      1323      1332      1341      1350
AGC TAT GTG AGA CCC TCC CAG TGG TCA TCC ATC CGC CTG TGG ACA AGC CCC ACC
-----
S   Y   V   R   P   S   Q   W   S   S   I   R   L   W   T   S   P   T

      1359      1368      1377      1386      1395      1404
TTC CAG TGG CTG ATC CCC GAC AGC GCT GAC ACC ACA GCT ACA CCC ACG CAC TGT
-----
F   Q   W   L   I   P   D   S   A   D   T   T   A   T   P   T   H   C

      1413      1422      1431      1440      1449      1458
GCC TAT GAC AGG ATC GTG GTT GCA GGG ATG CTG CTC CGA GGG GCC GTT GTT CCC
-----
A   Y   D   R   I   V   V   A   G   M   L   L   R   G   A   V   V   P

      1467      1476      1485      1494      1503      1512
GAC TCG GCT CTT CCC TTT AAC TTC CAG GCT GCC TAT GGC CTG AGT GAC CAA CTG
-----
D   S   A   L   P   F   N   F   Q   A   A   Y   G   L   S   D   Q   L

      1521      1530      1539      1548      1557
GCC CAA GCC ATC AGT GAC CAC TAT CCA GTG GAG GTG ATG CTG AAG TGA 3'
-----
A   Q   A   I   S   D   H   Y   P   V   E   V   M   L   K   *

```

Fig. 15(D)
(Sheet 3 of 3)

70/113

pAS104

LOCUS PAS104.DNA 1560 bp mRNA PRI 06-MAR-1995
 DEFINITION Humanised HMFG1 Fab'2 fused to human DNase I (pAS104)
 Position 924 G to A by ggg to gag
 Linker GR instead of GG (position 777)
 ACCESSION
 NID
 KEYWORDS DNase I.
 SOURCE DNase I sequence is from assembled oligos (thus modified c/f
 MHDNASE1.dna)
 ORGANISM Homo sapiens
 Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
 Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
 AUTHORS Shak, S., Capon, D.J., Hellmiss, R., Marsters, S.A. and Baker, C.L.
 TITLE Recombinant human DNase I reduces the viscosity of cystic
 fibrosis
 sputum
 JOURNAL Proc. Natl. Acad. Sci. U.S.A. 87 (23), 9188-9192 (1990)
 MEDLINE 91067672
 BASE COUNT 346 a 468 c 434 g 312 t
 ORIGIN

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1 ATGGGATGGA GCTGTATCAT CCTTCTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCAAGTGC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCGTGG TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CTTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAAC TCA
541 GCGGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAACTC ACACATGCTG TGTGGAGTGC CCACCGTGCC CAGCACCTGA AGGCAGGCTG
781 AAGATCGCAG CCTTCAACAT CCAGACATTT GGGGAGACCA AGATGTCCAA TGCCACCCTC
841 GTCAGCTACA TTGTGCAGAT CCTGAGCCGC TACGACATCG CCCTGGTCCA GGAGGT CAGA
901 GACAGCCACC TGA CTGCGGT GGAGAGCTG CTGGACAACC TCAATCAGGA CGCACCAGAC
961 ACCTATCACT ACGTGGTCAG TGAGCCACTG GGACGGAACA GCTATAAGGA GCGCTACCTG
1021 TTCGTGTACA GGCCTGACCA GGTGTCTGCG GTGGACAGCT ACTACTACGA TGATGGCTGC
1081 GAGCCCTGCG GGAACGACAC CTTCAACCGA GAGCCAGCCA TTGT CAGGTT CTTCTCCCGG
1141 TTCACAGAGG TCAGGGAGTT TGCCATTGTT CCCCTGCATG CGGCCCCGGG GGACGCAGTA
1201 GCCGAGATCG ACGCTCTCTA TGACGTCTAC CTGGATGTCC AAGAGAAATG GGGCTTGAG
1261 GACGTCATGT TGATGGGCGA CTTCAATGCG GGCTGCAGCT ATGTGAGACC CTCCCAGTGG
1321 TCATCCATCC GCCTGTGGAC AAGCCCCACC TTCCAGTGGC TGATCCCCGA CAGCGCTGAC
1381 ACCACAGCTA CACCCACGCA CTGTGCCATAT GACAGGATCG TGGTTGCAGG GATGCTGCTC
1441 CGAGGGGCGG TTGTTCCCGA CTCGGCTCTT CCCTTTAACT TCCAGGCTGC CTATGGCCTG
1501 AGTGACCAAC TGGCCCAGC CATCAGTGAC CACTATCCAG TGGAGGTGAT GCTGAAGTGA

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//

Fig. 16(A)

71/113

LOCUS FDDNASE104 1560 BP SS-DNA SYN 25-AUG-2000

DEFINITION -

ACCESSION -

KEYWORDS -

SOURCE -

FEATURES

Location/Qualifiers

frag join(1..>720,<793..1560)

/note="1 to 1560 of PAS104.dna [Split]"

frag 721..792

/note="1 to 72 of 104linker"

frag join(721..>774,<776..792)

/note="1 to 72 of 103linker [Split]"

frag join(721..>771,<772..>774,<776..792)

/note="1 to 78 of 102linker [Split]"

BASE COUNT 346 A 467 C 434 G 313 T 0 OTHER

ORIGIN -

1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG

61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC

121 TGCAAGGCTT CTGGCTACAC CTTCACTGCC TACTGGATAG AGTGGGTGCG CCAGGCTCCA

181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT

241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG

301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC

361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC

421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG

481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAAGTCA

541 GGCGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC

601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC

661 AACGTGAATC ACAAGCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT

721 GACAAAATC ACACATGCTG TGTCGAGTGT CCACCGTGTC CAGCACCAGA GGCAGGCTG

781 AAGATCGCAG CCTTCAACAT CCAGACATTT GGGGAGACCA AGATGTCCAA TGCCACCCTC

841 GTCAGTACA TTGTGCAGAT CCTGAGCCGC TACGACATCG CCCTGGTCCA GGAGGTCAGA

901 GACAGCCACC TGAATGCCGT GGAGAAAGCTG CTGGACAACC TCAATCAGGA CGCACCAGAC

961 ACCTATCACT ACGTGGTCAG TGAGCCACTG GGACGGAACA GCTATAAGGA GCGCTACCTG

1021 TTCGTGTACA GGCCTGACCA GGTGTCTGCG GTGGACAGCT ACTACTACGA TGATGGCTGC

1081 GAGCCCTGCG GGAACGACAC CTTCAACCGA GAGCCAGCCA TTGTCAAGTT CTTCTCCCGG

1141 TTCACAGAGG TCAGGGAGTT TGCCATTGTT CCCCTGCATG CGGCCCCGGG GGACGCAGTA

1201 GCCGAGATCG ACGCTCTCTA TGACGTCTAC CTGGATGTCC AAGAGAAATG GGGCTTGGAG

1261 GACGTCATGT TGATGGGCGA CTTCAATGCG GGCTGCAGCT ATGTGAGACC CTCCCAGTGG

1321 TCATCCATCC GCCTGTGGAC AAGCCCCACC TTCCAGTGGC TGATCCCCGA CAGCGCTGAC

1381 ACCACAGCTA CACCCACGCA CTGTGCCTAT GACAGGATCG TGGTTGCAGG GATGCTGCTC

1441 CGAGGGGCCG TTGTTCCCGA CTCGGCTCTT CCCTTTAACT TCCAGGCTGC CTATGGCCTG

1501 AGTGACCAAC TGGCCCAAGC CATCAGTGAC CACTATCCAG TGGAGGTGAT GCTGAAGTGA

Fig. 16(B)

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```

      9      18      27      36      45      54
5' ATG GGA TGG AGC TGT ATC ATC CTC TTC TTG GTA GCA ACA GCT ACA GGT GTC CAC
   ---
   M G W S C I I L F L V A T A T G V H

      63      72      81      90      99      108
TCC CAG GTG CAG CTG GTG CAG TCT GGG GCA GAG GTG AAA AAG CCT GGG GCC TCA
   ---
   S Q V Q L V Q S G A E V K K P G A S

      117      126      135      144      153      162
GTG AAG GTG TCC TGC AAG GCT TCT GGC TAC ACC TTC AGT GCC TAC TGG ATA GAG
   ---
   V K V S C K A S G Y T F S A Y W I E

      171      180      189      198      207      216
TGG GTG CGC CAG GCT CCA GGA AAG GGC CTC GAG TGG GTC GGA GAG ATT TTA CCT
   ---
   W V R Q A P G K G L E W V G E I L P

      225      234      243      252      261      270
GGA AGT AAT AAT TCT AGA TAC AAT GAG AAG TTC AAG GGC CGA GTG ACA GTC ACT
   ---
   G S N N S R Y N E K F K G R V T V T

      279      288      297      306      315      324
AGA GAC ACA TCC ACA AAC ACA GCC TAC ATG GAG CTC AGC AGC CTG AGG TCT GAG
   ---
   R D T S T N T A Y M E L S S L R S E

      333      342      351      360      369      378
GAC ACA GCC GTC TAT TAC TGT GCA AGA TCC TAC GAC TTT GCC TGG TTT GCT TAC
   ---
   D T A V Y Y C A R S Y D F A W F A Y

      387      396      405      414      423      432
TGG GGC CAA GGG ACT CTG GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG
   ---
   W G Q G T L V T V S S A S T K G P S

      441      450      459      468      477      486
GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC CTG
   ---
   V F P L A P S S K S T S G G T A A L

      495      504      513      522      531      540
GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA
   ---
   G C L V K D Y F P E P V T V S W N S

      549      558      567      576      585      594
GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA
   ---
   G A L T S G V H T F P A V L Q S S G

```

Fig. 16(C)
(Sheet 1 of 3)

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603	612	621	630	639	648
CTC TAC TCC CTC AGC	AGC GTG GTG ACC	GTG CCC TCC AGC	AGC TTG GGC ACC	CAG	
---	---	---	---	---	---
L Y S L S S V V T V P S S S L G T Q					
657	666	675	684	693	702
ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA					
---	---	---	---	---	---
T Y I C N V N H K P S N T K V D K K					
711	720	729	738	747	756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC TGT GTG GAG TGC CCA CCG					
---	---	---	---	---	---
V E P K S C D K T H T C C V E C P P					
765	774	783	792	801	810
TGC CCA GCA CCT GAA GGC AGG CTG AAG ATC GCA GCC TTC AAC ATC CAG ACA TTT					
---	---	---	---	---	---
C P A P E G R L K I A A F N I Q T F					
819	828	837	846	855	864
GGG GAG ACC AAG ATG TCC AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG ATC CTG					
---	---	---	---	---	---
G E T K M S N A T L V S Y I V Q I L					
873	882	891	900	909	918
AGC CGC TAC GAC ATC GCC CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG ACT GCC					
---	---	---	---	---	---
S R Y D I A L V Q E V R D S H L T A					
927	936	945	954	963	972
GTG GAG AAG CTG CTG GAC AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT CAC TAC					
---	---	---	---	---	---
V E K L L D N L N Q D A P D T Y H Y					
981	990	999	1008	1017	1026
GTG GTC AGT GAG CCA CTG GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG TTC GTG					
---	---	---	---	---	---
V V S E P L G R N S Y K E R Y L F V					
1035	1044	1053	1062	1071	1080
TAC AGG CCT GAC CAG GTG TCT GCG GTG GAC AGC TAC TAC TAC GAT GAT GGC TGC					
---	---	---	---	---	---
Y R P D Q V S A V D S Y Y Y D D G C					
1089	1098	1107	1116	1125	1134
GAG CCC TGC GGG AAC GAC ACC TTC AAC CGA GAG CCA GCC ATT GTC AGG TTC TTC					
---	---	---	---	---	---
E P C G N D T F N R E P A I V R F F					
1143	1152	1161	1170	1179	1188
TCC CGG TTC ACA GAG GTC AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG GCC CCG					
---	---	---	---	---	---
S R F T E V R E F A I V P L H A A P					
1197	1206	1215	1224	1233	1242

Fig. 16(C)
(Sheet 2 of 3)

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GGG GAC GCA GTA GCC GAG ATC GAC GCT CTC TAT GAC GTC TAC CTG GAT GTC CAA
---
G   D   A   V   A   E   I   D   A   L   Y   D   V   Y   L   D   V   Q

      1251      1260      1269      1278      1287      1296
GAG AAA TGG GGC TTG GAG GAC GTC ATG TTG ATG GGC GAC TTC AAT GCG GGC TGC
---
E   K   W   G   L   E   D   V   M   L   M   G   D   F   N   A   G   C

      1305      1314      1323      1332      1341      1350
AGC TAT GTG AGA CCC TCC CAG TGG TCA TCC ATC CGC CTG TGG ACA AGC CCC ACC
---
S   Y   V   R   P   S   Q   W   S   S   I   R   L   W   T   S   P   T

      1359      1368      1377      1386      1395      1404
TTC CAG TGG CTG ATC CCC GAC AGC GCT GAC ACC ACA GCT ACA CCC ACG CAC TGT
---
F   Q   W   L   I   P   D   S   A   D   T   T   A   T   P   T   H   C

      1413      1422      1431      1440      1449      1458
GCC TAT GAC AGG ATC GTG GTT GCA GGG ATG CTG CTC CGA GGG GCC GTT GTT GCC
---
A   Y   D   R   I   V   V   A   G   M   L   L   R   G   A   V   V   P

      1467      1476      1485      1494      1503      1512
GAC TCG GCT CTT CCC TTT AAC TTC CAG GCT GCC TAT GGC CTG AGT GAC CAA CTG
---
D   S   A   L   P   F   N   F   Q   A   A   Y   G   L   S   D   Q   L

      1521      1530      1539      1548      1557
GCC CAA GCC ATC AGT GAC CAC TAT CCA GTG GAG GTG ATG CTG AAG TGA 3'
---
A   Q   A   I   S   D   H   Y   P   V   E   V   M   L   K   *

```

Fig. 16(C)
(Sheet 3 of 3)

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pAS105

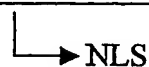
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 ACCESSION
 NID
 KEYWORDS DNase I.
 SOURCE DNase I sequence is from assembled oligos (thus modified c/f
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 ORGANISM Homo sapiens
 Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
 Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
 AUTHORS Shak, S., Capon, D.J., Hellmiss, R., Marsters, S.A. and Baker, C.L.
 TITLE Recombinant human DNase I reduces the viscosity of cystic
 fibrosis
 sputum
 JOURNAL Proc. Natl. Acad. Sci. U.S.A. 87 (23), 9188-9192 (1990)
 MEDLINE 91067672
 BASE COUNT 353 a 473 c 442 g 310 t
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121 TGCAAGGCTT CTGGCTACAC CTTCACTGCC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTGCTCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAACCTCA
541 GCGGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAAACTC ACACATGCCC ACCGTGCCCC GCACCTGAAG GCGGGCTGAA GATCGCAGCC
781 TTCAACATCC AGACATTGGG GGAGACCAAG ATGTCCAATG CCACCTCGT CAGCTACATT
841 GTGCAGATCC TGAGCCGCTA CGACATCGCC CTGGTCCAGG AGGTCAGAGA CAGCCACCTG
901 ACTGCCGTGG GGAAGCTGCT GGACAACCTC AATCAGGACG CACCAGACAC CTATCACTAC
961 GTGGTCAGTG AGCCACTGGG ACGGAACAGC TATAAGGAGC GCTACCTGTT CGGTACAGG
1021 CCTGACCAGG TGTCTGCGGT GGACAGCTAC TACTACGATG ATGGCTGCGA GCCCTGCGGG
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1381 CCCACGCACT GTGCCATGA CAGGATCGTG GTTGCAAGGA TGCTGCTCCG AGGGGCCGTT
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1501 GCCCAAGCCA TCAGTGACCA CTATCCAGTG GAGGTGATGC TGAAGGGGGG CGGACCCAAA
1561 AAGAAGCGCA AGGTTTGA

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 NLS
Fig. 17(A)

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 DEFINITION -
 ACCESSION -
 KEYWORDS -
 SOURCE -
 FEATURES Location/Qualifiers
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 /note="1 to 80 of 102linker [Split]"
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 181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
 241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
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 841 GTGCAGATCC TGAGCCGCTA CGACATCGCC CTGGTCCAGG AGGTCAGAGA CAGCCACCTG
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 1201 GCTCTCTATG ACGTCTACCT GGATGTCCAA GAGAAATGGG GCTTGGAGGA CGTCATGTTG
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 1381 CCCACGCACT GTGCCTATGA CAGGATCGTG GTTGCAGGGA TGCTGCTCCG AGGGGCCGTT
 1441 GTTCCCGACT CGGCTCTTCC CTTTAACTTC CAGGCTGCCT ATGGCCTGAG TGACCAACTG
 1501 GCCCAAGCCA TCAGTGACCA CTATCCAGTG GAGGTGATGC TGAAGGGGGG CGGACCCAAA
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Fig. 17(B)

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LOCUS FDDNASE105 1587 BP SS-DNA SYN 29-AUG-2000

DEFINITION -

ACCESSION -

KEYWORDS -

SOURCE -

FEATURES Location/Qualifiers
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 /note="1 to 1578 of PAS105.dna [Split]"
 frag 730..789
 /note="1 to 60 of 101/105linker"
 frag join(730..>744,<745..>768,<769..>789)
 /note="1 to 80 of 102linker [Split]"

BASE COUNT 354 A 477 C 445 G 311 T 0 OTHER

ORIGIN -

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121 AAGGTGTCTT GCAAGGCTTC TGGCTACACC TTCAGTGCCT ACTGGATAGA GTGGGTGCGC
181 CAGGCTCCAG GAAAGGGCCT CGAGTGGGTC GGAGAGATTT TACCTGGAAG TAATAATTCT
241 AGATACAATG AGAAGTTCAA GGGCCGAGTG ACAGTCACTA GAGACACATC CACAAACACA
301 GCCTACATGG AGCTCAGCAG CCTGAGGTCT GAGGACACAG CCGTCTATTA CTGTGCAAGA
361 TCCTACGACT TTGCCTGGTT TGCTTACTGG GGCCAAGGGA CTCTGGTCAC AGTCTCCTCA
421 GCCTCCACCA AGGGCCCATC GGTCTTCCCC CTGGCACCCCT CCTCCAAGAG CACCTCTGGG
481 GGCACAGCGG CCCTGGGCTG CCTGGTCAAG GACTACTTCC CCGAACCGGT GACGGTGTCTG
541 TGGAACTCAG GCGCCCTGAC CAGCGGCGTG CACACCTTCC CGGCTGTCCT ACAGTCCTCA
601 GGACTCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAGCTTGGG CACCCAGACC
661 TACATCTGCA ACGTGAATCA CAAGCCCAGC AACACCAAGG TGGACAAGAA AGTTGAGCCC
721 AAATCTTGTG ACAAACCTCA CACATGTCCA CCGTGTCCAG CACCAGAGGG CGGGCTGAAG
781 ATCGCAGCCT TCAACATCCA GACATTGGG GAGACCAAGA TGTCCAATGC CACCCTCGTC
841 AGCTACATTG TGCAGATCCT GAGCCGCTAC GACATCGCCC TGGTCCAGGA GGTCAGAGAC
901 AGCCACCTGA CTGCCGTGGG GAAGCTGCTG GACAACCTCA ATCAGGACGC ACCAGACACC
961 TATCACTACG TGGTCAGTGA GCCACTGGGA CGGAACAGCT ATAAGGAGCG CTACCTGTTC
1021 GTGTACAGGC CTGACCAGGT GTCTGCGGTG GACAGCTACT ACTACGATGA TGGCTGCGAG
1081 CCTGCGGGA ACGACACCTT CAACCGAGAG CCAGCCATTG TCAGGTTCTT CTCCCGGTTT
1141 ACAGAGGTCA GGGAGTTTGC CATTGTTCCC CTGCATGCGG CCCCAGGGGA CGCAGTAGCC
1201 GAGATCGACG CTCTCTATGA CGTCTACCTG GATGTCCAAG AGAAATGGGG CTTGGAGGAC
1261 GTCATGTTGA TGGGCGACTT CAATGCGGGC TGCAGCTATG TGAGACCTC CCAGTGGTCA
1321 TCCATCCGCC TGTGGACAAG CCCCACCTTC CAGTGGCTGA TCCCCGACAG CGCTGACACC
1381 ACAGCTACAC CCACGCACTG TGCCTATGAC AGGATCGTGG TTGCAGGGAT GCTGCTCCGA
1441 GGGGCCGTTG TTCCCGACTC GGCTCTTCCC TTAACTTCC AGGCTGCCTA TGGCCTGAGT
1501 GACCAACTGG CCCAAGCCAT CAGTGACCAC TATCCAGTGG AGGTGATGCT GAAGGGGGGC
1561 GGACCCAAAA AGAAGCGCAA GGTTTGA

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Fig. 17(C)

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```

      9      18      27      36      45      54
5' ATG GGA TGG AGC TGT ATC ATC CTC TTC TTG GTA GCA ACA GCT ACA GGT GTC CAC
-----
    M  G  W  S  C  I  I  L  F  L  V  A  T  A  T  G  V  H

      63      72      81      90      99     108
TCC CAG GTG CAG CTG GTG CAG TCT GGG GCA GAG GTG AAA AAG CCT GGG GCC TCA
-----
    S  Q  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  A  S

      117     126     135     144     153     162
GTG AAG GTG TCC TGC AAG GCT TCT GGC TAC ACC TTC AGT GCC TAC TGG ATA GAG
-----
    V  K  V  S  C  K  A  S  G  Y  T  F  S  A  Y  W  I  E

      171     180     189     198     207     216
TGG GTG CGC CAG GCT CCA GGA AAG GGC CTC GAG TGG GTC GGA GAG ATT TTA CCT
-----
    W  V  R  Q  A  P  G  K  G  L  E  W  V  G  E  I  L  P

      225     234     243     252     261     270
GGA AGT AAT AAT TCT AGA TAC AAT GAG AAG TTC AAG GGC CGA GTG ACA GTC ACT
-----
    G  S  N  N  S  R  Y  N  E  K  F  K  G  R  V  T  V  T

      279     288     297     306     315     324
AGA GAC ACA TCC ACA AAC ACA GCC TAC ATG GAG CTC AGC AGC CTG AGG TCT GAG
-----
    R  D  T  S  T  N  T  A  Y  M  E  L  S  S  L  R  S  E

      333     342     351     360     369     378
GAC ACA GCC GTC TAT TAC TGT GCA AGA TCC TAC GAC TTT GCC TGG TTT GCT TAC
-----
    D  T  A  V  Y  Y  C  A  R  S  Y  D  F  A  W  F  A  Y

      387     396     405     414     423     432
TGG GGC CAA GGG ACT CTG GTG ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG
-----
    W  G  Q  G  T  L  V  T  V  S  S  A  S  T  K  G  P  S

      441     450     459     468     477     486
GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC CTG
-----
    V  F  P  L  A  P  S  S  K  S  T  S  G  G  T  A  A  L

      495     504     513     522     531     540
GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA
-----
    G  C  L  V  K  D  Y  F  P  E  P  V  T  V  S  W  N  S

      549     558     567     576     585     594
GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA
-----
    G  A  L  T  S  G  V  H  T  F  P  A  V  L  Q  S  S  G

```

Fig. 17(D)
(Sheet 1 of 3)

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603	612	621	630	639	648
CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG					
L Y S L S S V V T V P S S S L G T Q					
657	666	675	684	693	702
ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA					
T Y I C N V N H K P S N T K V D K K					
711	720	729	738	747	756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG TGC CCA GCA CCT					
V E P K S C D K T H T C P P C P A P					
765	774	783	792	801	810
GAA GGC GGG CTG AAG ATC GCA GCC TTC AAC ATC CAG ACA TTT GGG GAG ACC AAG					
E G G L K I A A F N I Q T F G E T K					
819	828	837	846	855	864
ATG TCC AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG ATC CTG AGC CGC TAC GAC					
M S N A T L V S Y I V Q I L S R Y D					
873	882	891	900	909	918
ATC GCC CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG ACT GCC GTG GGG AAG CTG					
I A L V Q E V R D S H L T A V G K L					
927	936	945	954	963	972
CTG GAC AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT CAC TAC GTG GTC AGT GAG					
L D N L N Q D A P D T Y H Y V V S E					
981	990	999	1008	1017	1026
CCA CTG GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG TTC GTG TAC AGG CCT GAC					
P L G R N S Y K E R Y L F V Y R P D					
1035	1044	1053	1062	1071	1080
CAG GTG TCT GCG GTG-GAC AGC TAC TAC TAC GAT GAT GGC TGC GAG CCC TGC GGG					
Q V S A V D S Y Y Y D D G C E P C G					
1089	1098	1107	1116	1125	1134
AAC GAC ACC TTC AAC CGA GAG CCA GCC ATT GTG AGG TTC TTC TCC CGG TTC ACA					
N D T F N R E P A I V R F F S R F T					
1143	1152	1161	1170	1179	1188
GAG GTC AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG GCC CCG GGG GAC GCA GTA					
E V R E F A I V P L H A A P G D A V					
1197	1206	1215	1224	1233	1242

Fig. 17(D)
(Sheet 2 of 3)

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```

GCC GAG ATC GAC GCT CTC TAT GAC GTC TAC CTG GAT GTC CAA GAG AAA TGG GGC
-----
A   E   I   D   A   L   Y   D   V   Y   L   D   V   Q   E   K   W   G

      1251      1260      1269      1278      1287      1296
TTG GAG GAC GTC ATG TTG ATG GGC GAC TTC AAT GCG GGC TGC AGC TAT GTG AGA
-----
L   E   D   V   M   L   M   G   D   F   N   A   G   C   S   Y   V   R

      1305      1314      1323      1332      1341      1350
CCC TCC CAG TGG TCA TCC ATC CGC CTG TGG ACA AGC CCC ACC TTC CAG TGG CTG
-----
P   S   Q   W   S   S   I   R   L   W   T   S   P   T   F   Q   W   L

      1359      1368      1377      1386      1395      1404
ATC CCC GAC AGC GCT GAC ACC ACA GCT ACA CCC ACG CAC TGT GCC TAT GAC AGG
-----
I   P   D   S   A   D   T   T   A   T   P   T   H   C   A   Y   D   R

      1413      1422      1431      1440      1449      1458
ATC GTG GTT GCA GGG ATG CTG CTC CGA GGG GCC GTT GTT CCC GAC TCG GCT CTT
-----
I   V   V   A   G   M   L   L   R   G   A   V   V   P   D   S   A   L

      1467      1476      1485      1494      1503      1512
CCC TTT AAC TTC CAG GCT GCC TAT GGC CTG AGT GAC CAA CTG GCC CAA GCC ATC
-----
P   F   N   F   Q   A   A   Y   G   L   S   D   Q   L   A   Q   A   I

      1521      1530      1539      1548      1557      1566
AGT GAC CAC TAT CCA GTG GAG GTG ATG CTG AAG GGG GGC GGA CCC AAA AAG AAG
-----
S   D   H   Y   P   V   E   V   M   L   K   G   G   G   P   K   K   K

      1575
CGC AAG GTT TGA 3'
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R   K   V   *

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Fig. 17(D)
(Sheet 3 of 3)

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pAS106

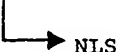
LOCUS PAS106.DNA 1596 bp mRNA PRI 06-MAR-1995
 DEFINITION Humanised HMFG1 Fab'2 fused to human DNase I with SV40
 NLS (pAS106)
 ACCESSION
 NID
 KEYWORDS DNase I.
 SOURCE DNase I sequence is from assembled oligos (thus modified c/f
 MHDNASE1.dna)
 ORGANISM Homo sapiens
 Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
 Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
 AUTHORS Shak, S., Capon, D.J., Hellmiss, R., Marsters, S.A. and Baker, C.L.
 TITLE Recombinant human DNase I reduces the viscosity of cystic
 fibrosis
 sputum
 JOURNAL Proc. Natl. Acad. Sci. U.S.A. 87 (23), 9188-9192 (1990)
 MEDLINE 91067672
 BASE COUNT 355 a 475 c 452 g 314 t
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1 ATGGGATGGA GCTGTATCAT CCTCTTCTTG GTAGCAACAG CTACAGGTGT CCACTCCCAG
61 GTGCAGCTGG TGCAGTCTGG GGCAGAGGTG AAAAAGCCTG GGGCCTCAGT GAAGGTGTCC
121 TGCAAGGCTT CTGGCTACAC CTTCACTGCC TACTGGATAG AGTGGGTGCG CCAGGCTCCA
181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG
481 GCCCTGGGCT GCCTGGTCAA GGACTIONTC CCCGAACCGG TGACGGTGTG GTGGAACTCA
541 GGCGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCTTC AGGACTCTAC
601 TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
661 AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGTTGAGCC CAAATCTTGT
721 GACAAAATC ACACATGCTG TGTGGAGTGC CCACCGTGCC CAGCACCTGA AGGGAGCGGC
781 GGGCTGAAGA TCGCAGCCTT CAACATCCAG ACATTTGGGG AGACCAAGAT GTCCAATGCC
841 ACCCTCGTCA GCTACATTGT GCAGATCCTG AGCCGCTACG ACATCGCCCT GGTCCAGGAG
901 GTCAGAGACA GCCACCTGAC TGCCGTGGGG AAGCTGCTGG ACAACCTCAA TCAGGACGCA
961 CCAGACACCT ATCACTACGT GGTCACTGAG CCACTGGGAC GGAACAGCTA TAAGGAGCGC
1021 TACCTGTTCG TGTACAGGCC TGACCAGGTG TCTGCGGTGG ACAGCTACTA CTACGATGAT
1081 GGCTGCGAGC CCTGCGGGAA CGACACCTTC AACCGAGAGC CAGCCATTGT CAGGTTCTTC
1141 TCCCGGTTCA CAGAGGTCAG GGAGTTTGCC ATTGTTCCCC TGCATGCGGC CCCGGGGGAC
1201 GCAGTAGCCG AGATCGACGC TCTCTATGAC GTCTACCTGG ATGTCCAAGA GAAATGGGGC
1261 TTGGAGGACG TCATGTTGAT GGGCGACTTC AATGCGGGCT GCAGCTATGT GAGACCTTCC
1321 CAGTGGTCAT CCATCCGCCT GTGGACAAGC CCCACCTTCC AGTGGCTGAT CCCCAGCAGC
1381 GCTGACACCA CAGCTACACC CACGCACTGT GCCTATGACA GGATCGTGGT TGCAGGGATG
1441 CTGCTCCGAG GGGCCGTTGT TCCGACTCG GCTCTTCCCT TTAACCTCCA GGCTGCCTAT
1501 GGCCTGAGTG ACCAACTGGC CCAAGCCATC AGTGACCACT ATCCAGTGA GGTGATGCTG
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Fig. 18(A)

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LOCUS FDDNASE106 1596 BP SS-DNA SYN 25-AUG-2000
 DEFINITION -
 ACCESSION -
 KEYWORDS -
 SOURCE -
 FEATURES Location/Qualifiers
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 /note="1 to 1596 of PAS106.dna [Split]"
 frag 721..798
 /note="1 to 78 of 102/106linker"
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 181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT
 241 GAGAAGTTCA AGGGCCGAGT GACAGTCACT AGAGACACAT CCACAAACAC AGCCTACATG
 301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC
 361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC
 421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGCACAGCG
 481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTG GTGGAACCTCA
 541 GGCGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC
 601 TCCCTCAGCA CCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC
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 721 GACAAAACCT ACACATGCTG TGTCGAGTGT CCACCGTGTG CAGCACCAGA GGGGAGCGGC
 781 GGGCTGAAGA TCGCAGCCTT CAACATCCAG ACATTGGGGG AGACCAAGAT GTCCAATGCC
 841 ACCCTCGTCA GCTACATTGT GCAGATCCTG AGCCGCTACG ACATCGCCCT GGTCCAGGAG
 901 GTCAGAGACA GCCACCTGAC TGCCGTGGGG AAGCTGCTGG ACAACCTCAA TCAGGACGCA
 961 CCAGACACCT ATCACTACGT GGTCACTGAG CCACTGGGAC GGAACAGCTA TAAGGAGCGC
 1021 TACCTGTTCG TGTACAGGCC TGACCAGGTG TCTGCGGTGG ACAGCTACTA CTACGATGAT
 1081 GGCTGCGAGC CCTGCGGGAA CGACACCTTC AACCAGAGAG CAGCCATTGT CAGGTTCTTC
 1141 TCCCGGTTCA CAGAGGTCAG GGAGTTTGCC ATTGTTCCCC TGCATGCGGC CCCGGGGGAC
 1201 GCAGTAGCCG AGATCGACGC TCTCTATGAC GTCTACCTGG ATGTCCAAGA GAAATGGGGC
 1261 TTGGAGGACG TCATGTTGAT GGGCGACTTC AATGCGGGCT GCAGCTATGT GAGACCCTCC
 1321 CAGTGGTCAT CCATCCGCCT GTGGACAAGC CCCACCTTCC AGTGGCTGAT CCCCAGACAGC
 1381 GCTGACACCA CAGCTACACC CACGCACTGT GCCTATGACA GGATCGTGGT TGCAGGGATG
 1441 CTGCTCCGAG GGGCCGTTGT TCCCGACTCG GCTCTTCCCT TTAACCTCCA GGCTGCCTAT
 1501 GGCCTGAGTG ACCAACTGGC CCAAGCCATC AGTGACCACT ATCCAGTGGA GGTGATGCTG
 1561 AAGGGGGGCG GACCCAAAAA GAAGCGCAAG GTTTGA

//

Fig. 18(B)

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LOCUS FDDNASE106 1605 BP SS-DNA SYN 29-AUG-2000
 DEFINITION -
 ACCESSION -
 KEYWORDS -
 SOURCE -
 FEATURES Location/Qualifiers
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 frag join(10..>729,<808..1605)
 /note="1 to 1596 of PAS106.dna [Split]"
 frag 730..807
 /note="1 to 78 of 102/106linker"
 BASE COUNT 356 A 480 C 454 G 315 T 0 OTHER
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 61 CACTCCCAGG TGCAGCTGGT GCAGTCTGGG GCAGAGGTGA AAAAGCCTGG GGCCTCAGTG
 121 AAGGTGTCCT GCAAGGCTTC TGGCTACACC TTCAGTGCCT ACTGGATAGA GTGGGTGCGC
 181 CAGGCTCCAG GAAAGGGCCT CGAGTGGGTC GGAGAGATTT TACCTGGAAG TAATAATTCT
 241 AGATACAATG AGAAGTTCAA GGGCCGAGTG ACAGTCACTA GAGACACATC CACAAACACA
 301 GCCTACATGG AGCTCAGCAG CCTGAGGTCT GAGGACACAG CCGTCTATTA CTGTGCAAGA
 361 TCCTACGACT TTGCCTGGTT TGCTTACTGG GGCCAAGGGA CTCTGGTCAC AGTCTCCTCA
 421 GCCTCCACCA AGGGCCCATC GGTCTTCCCC CTGGCACCCCT CCTCCAAGAG CACCTCTGGG
 481 GGCACAGCGG CCCTGGGCTG CCTGGTCAAG GACTACTTCC CCGAACCGGT GACGGTGTCTG
 541 TGGAACTCAG GCGCCCTGAC CAGCGGCGTG CACACCTTCC CGGCTGTCCT ACAGTCCTCA
 601 GGACTCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAGCTTGGG CACCCAGACC
 661 TACATCTGCA ACGTGAATCA CAAGCCAGC AACACCAAGG TGGACAAGAA AGTTGAGCCC
 721 AAATCTTGTG ACAAACTCA CACATGCTGT GTCGAGTGTC CACCGTGTCC AGCACCAGAG
 781 GGGAGCGGCG GGCTGAAGAT CGCAGCCTTC AACATCCAGA CATTTGGGGA GACCAAGATG
 841 TCCAATGCCA CCCTCGTCAG CTACATTGTG CAGATCCTGA GCCGCTACGA CATCGCCCTG
 901 GTCCAGGAGG TCAGAGACAG CCACCTGACT GCCGTGGGGA AGCTGCTGGA CAACCTCAAT
 961 CAGGACGCAC CAGACACCTA TCACTACGTG GTCAGTGAGC CACTGGGACG GAACAGCTAT
 1021 AAGGAGCGCT ACCTGTTCGT GTACAGGCCT GACCAGGTGT CTGCGGTGGA CAGCTACTAC
 1081 TACGATGATG GCTGCGAGCC CTGCGGGAAC GACACCTTCA ACCGAGAGCC AGCCATTGTC
 1141 AGGTTCTTCT CCCGGTTCAC AGAGGTCAGG GAGTTTGCCA TTGTTCCCCT GCATGCGGCC
 1201 CCGGGGGACG CAGTAGCCGA GATCGACGCT CTCTATGACG TCTACCTGGA TGTCCAAGAG
 1261 AAATGGGGCT TGGAGGACGT CATGTTGATG GCGGACTTCA ATGCGGGCTG CAGCTATGTG
 1321 AGACCTCCC AGTGGTCATC CATCCGCTG TGGACAAGCC CCACCTTCCA GTGGCTGATC
 1381 CCCGACAGCG CTGACACCAC AGCTACACCC ACGCACTGTG CCTATGACAG GATCGTGGTT
 1441 GCAGGGATGC TGCTCCGAGG GGCGTTGTT CCCGACTCGG CTCTTCCCTT TAACTTCCAG
 1501 GCTGCCTATG GCCTGAGTGA CCAACTGGCC CAAGCCATCA GTGACCACTA TCCAGTGGAG
 1561 GTGATGCTGA AGGGGGGCGG ACCCAAAAAG AAGCGCAAGG TTTGA

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Fig. 18(C)

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9	18	27	36	45	54
ATG GGA TGG AGC TGT ATC ATC CTC TTC TTG GTA GCA ACA GCT ACA GGT GTC CAC					

M G W S C I I L F L V A T A T G V H					
63	72	81	90	99	108
TCC CAG GTG CAG CTG GTG CAG TCT GGG GCA GAG GTG AAA AAG CCT GGG GCC TCA					

S Q V Q L V Q S G A E V K K P G A S					
117	126	135	144	153	162
GTG AAG GTG TCC TGC AAG GCT TCT GGC TAC ACC TTC AGT GCC TAC TGG ATA GAG					

V K V S C K A S G Y T F S A Y W I E					
171	180	189	198	207	216
TGG GTG CGC CAG GCT CCA GGA AAG GGC CTC GAG TGG GTC GGA GAG ATT TTA CCT					

W V R Q A P G K G L E W V G E I L P					
225	234	243	252	261	270
GGA AGT AAT AAT TCT AGA TAC AAT GAG AAG TTC AAG GGC CGA GTG ACA GTC ACT					

G S N N S R Y N E K F K G R V T V T					
279	288	297	306	315	324
AGA GAC ACA TCC ACA AAC ACA GCC TAC ATG GAG CTC AGC AGC CTG AGG TCT GAG					

R D T S T N T A Y M E L S S L R S E					
333	342	351	360	369	378
GAC ACA GCC GTC TAT TAC TGT GCA AGA TCC TAC GAC TTT GCC TGG TTT GCT TAC					

D T A V Y Y C A R S Y D F A W F A Y					
387	396	405	414	423	432
TGG GGC CAA GGG ACT CTG GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG					

W G Q G T L V T V S S A S T K G P S					
441	450	459	468	477	486
GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC CTG					

V F P L A P S S K S T S G G T A A L					
495	504	513	522	531	540
GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA					

G C L V K D Y F P E P V T V S W N S					
549	558	567	576	585	594
GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA					

G A L T S G V H T F P A V L Q S S G					

Fig. 18(C)
(Sheet 1 of 3)

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603	612	621	630	639	648
CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG					
L Y S L S S V V T V P S S S L G T Q					
657	666	675	684	693	702
ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA					
T Y I C N V N H K P S N T K V D K K					
711	720	729	738	747	756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC TGT GTG GAG TGC CCA CCG					
V E P K S C D K T H T C C V E C P P					
765	774	783	792	801	810
TGC CCA GCA CCT GAA GGG AGC GGC GGG CTG AAG ATC GCA GCC TTC AAC ATC CAG					
C P A P E G S G G L K I A A F N I Q					
819	828	837	846	855	864
ACA TTT GGG GAG ACC AAG ATG TCC AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG					
T F G E T K M S N A T L V S Y I V Q					
873	882	891	900	909	918
ATC CTG AGC CGC TAC GAC ATC GCC CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG					
I L S R Y D I A L V Q E V R D S H L					
927	936	945	954	963	972
ACT GCC GTG GGG AAG CTG CTG GAC AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT					
T A V G K L L D N L N Q D A P D T Y					
981	990	999	1008	1017	1026
CAC TAC GTG GTC AGT GAG CCA CTG GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG					
H Y V V S E P L G R N S Y K E R Y L					
1035	1044	1053	1062	1071	1080
TTC GTG TAC AGG CCT GAC CAG GTG TCT GCG GTG GAC AGC TAC TAC TAC GAT GAT					
F V Y R P D Q V S A V D S Y Y Y D D					
1089	1098	1107	1116	1125	1134
GGC TGC GAG CCC TGC GGG AAC GAC ACC TTC AAC CGA GAG CCA GCC ATT GTC AGG					
G C E P C G N D T F N R E P A I V R					
1143	1152	1161	1170	1179	1188
TTC TTC TCC CGG TTC ACA GAG GTC AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG					
F F S R F T E V R E F A I V P L H A					
1197	1206	1215	1224	1233	1242

Fig. 18(C)
(Sheet 2 of 3)

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GCC CCG GGG GAC GCA GTA GCC GAG ATC GAC GCT CTC TAT GAC GTC TAC CTG GAT
---
A P G D A V A E I D A L Y D V Y L D

      1251      1260      1269      1278      1287      1296
GTC CAA GAG AAA TGG GGC TTG GAG GAC GTC ATG TTG ATG GGC GAC TTC AAT GCG
---
V Q E K W G L E D V M L M G D F N A

      1305      1314      1323      1332      1341      1350
GGC TGC AGC TAT GTG AGA CCC TCC CAG TGG TCA TCC ATC CGC CTG TGG ACA AGC
---
G C S Y V R P S Q W S S I R L W T S

      1359      1368      1377      1386      1395      1404
CCC ACC TTC CAG TGG CTG ATC CCC GAC AGC GCT GAC ACC ACA GCT ACA CCC ACG
---
P T F Q W L I P D S A D T T A T P T

      1413      1422      1431      1440      1449      1458
CAC TGT GCC TAT GAC AGG ATC GTG GTT GCA GGG ATG CTG CTC CGA GGG GCC GTT
---
H C A Y D R I V V A G M L L R G A V

      1467      1476      1485      1494      1503      1512
GTT CCC GAC TCG GCT CTT CCC TTT AAC TTC CAG GCT GCC TAT GGC CTG AGT GAC
---
V P D S A L P F N F Q A A Y G L S D

      1521      1530      1539      1548      1557      1566
CAA CTG GCC CAA GCC ATC AGT GAC CAC TAT CCA GTG GAG GTG ATG CTG AAG GGG
---
Q L A Q A I S D H Y P V E V M L K G

      1575      1584      1593
GGC GGA CCC AAA AAG AAG CGC AAG GTT TGA 3'
---
G G P K K K R K V *
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Fig. 18(C)
(Sheet 3 of 3)

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pAS107

LOCUS PAS107.DNA 1590 bp mRNA PRI 06-MAR-1995
 DEFINITION Humanised HMFG1 Fab'2 fused to human DNase I with SV40
 NLS (pAS107)
 ACCESSION
 NID
 KEYWORDS DNase I.
 SOURCE DNase I sequence is from assembled oligos (thus modified c/f
 MHDNASE1.dna)
 ORGANISM Homo sapiens
 Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
 Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
 AUTHORS Shak,S., Capon,D.J., Hellmiss,R., Marsters,S.A. and Baker,C.L.
 TITLE Recombinant human DNase I reduces the viscosity of cystic
 fibrosis
 sputum
 JOURNAL Proc. Natl. Acad. Sci. U.S.A. 87 (23), 9188-9192 (1990)
 MEDLINE 91067672
 BASE COUNT 354 a 474 c 448 g 314 t
 ORIGIN

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1321 TCATCCATCC GCCTGTGGAC AAGCCCCACC TTCCAGTGGC TGATCCCCGA CAGCGCTGAC
1381 ACCACAGCTA CACCCACGCA CTGTGCCTAT GACAGGATCG TGGTTGCAGG GATGCTGCTC
1441 CGAGGGGCGG TTGTTCCCGA CTCGGCTCTT CCCTTTAACT TCCAGGCTGC CTATGGCCTG
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1561 GCGGGACCCA AAAAGAAGCG CAAGGTTTGA

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Fig. 19(A)

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LOCUS FDDNASE107 1590 BP SS-DNA SYN 25-AUG-2000

DEFINITION -

ACCESSION -

KEYWORDS -

SOURCE -

FEATURES

Location/Qualifiers

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/note="1 to 1590 of PAS107.dna [Split]"

frag 721..792

/note="1 to 72 of 103/107linker"

frag join(721..>771,<772..792)

/note="1 to 78 of 102linker [Split]"

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181 GGAAAGGGCC TCGAGTGGGT CGGAGAGATT TTACCTGGAA GTAATAATTC TAGATACAAT

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301 GAGCTCAGCA GCCTGAGGTC TGAGGACACA GCCGTCTATT ACTGTGCAAG ATCCTACGAC

361 TTTGCCTGGT TTGCTTACTG GGGCCAAGGG ACTCTGGTCA CAGTCTCCTC AGCCTCCACC

421 AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG

481 GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAAGTCA

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1081 GAGCCCTGCG GGAACGACAC CTTCAACCGA GAGCCAGCCA TTGTCAAGTT CTTCTCCCGG

1141 TTCACAGAGG TCAGGGAGTT TGCCATTGTT CCCCTGCATG CGGCCCCGGG GGACGCAGTA

1201 GCCGAGATCG ACGCTCTCTA TGACGTCTAC CTGGATGTCC AAGAGAAATG GGGCTTGGAG

1261 GACGTCATGT TGATGGGCGA CTTCAATGCG GGCTGCAGCT ATGTGAGACC CTCCCAGTGG

1321 TCATCCATCC GCCTGTGGAC AAGCCCCACC TTCCAGTGGC TGATCCCCGA CAGCGCTGAC

1381 ACCACAGCTA CACCCACGCA CTGTGCCTAT GACAGGATCG TGGTTGCAGG GATGCTGCTC

1441 CGAGGGGCGG TTGTTCCCGA CTCGGCTCTT CCCTTTAACT TCCAGGCTGC CTATGGCCTG

1501 AGTGACCAAC TGGCCCAAGC CATCAGTGAC CACTATCCAG TGGAGGTGAT GCTGAAGGGG

1561 GGCGGACCCA AAAAGAAGCG CAAGGTTTGA

//

Fig. 19(B)

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LOCUS FDDNASE107 1599 BP SS-DNA SYN 29-AUG-2000
 DEFINITION -
 ACCESSION -
 KEYWORDS -
 SOURCE -
 FEATURES
 Location/Qualifiers
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 /note="1 to 1590 of PAS107.dna [Split]"
 frag 730..801
 /note="1 to 72 of 103/107linker"
 frag join(730..>780,<781..801)
 /note="1 to 78 of 102linker [Split]"
 BASE COUNT 355 A 479 C 450 G 315 T 0 OTHER
 ORIGIN -
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 61 CACTCCCAGG TGCAGCTGGT GCAGTCTGGG GCAGAGGTGA AAAAGCCTGG GGCCTCAGTG
 121 AAGGTGTCCT GCAAGGCTTC TGGCTACACC TTCAGTGCCT ACTGGATAGA GTGGGTGCGC
 181 CAGGCTCCAG GAAAGGGCCT CGAGTGGGTC GGAGAGATTT TACCTGGAAG TAATAATTCT
 241 AGATACAATG AGAAGTTCAA GGGCCGAGTG ACAGTCACTA GAGACACATC CACAAACACA
 301 GCCTACATGG AGCTCAGCAG CCTGAGGTCT GAGGACACAG CCGTCTATTA CTGTGCAAGA
 361 TCCTACGACT TTGCCTGGTT TGCTTACTGG GGCCAAGGGA CTCTGGTCAC AGTCTCCTCA
 421 GCCTCCACCA AGGGCCCCATC GGTCTTCCCC CTGGCACCCCT CCTCCAAGAG CACCTCTGGG
 481 GGCACAGCGG CCCTGGGCTG CCTGGTCAAG GACTACTTCC CCGAACCGGT GACGGTGTCTG
 541 TGGAACTCAG GCGCCCTGAC CAGCGGCGTG CACACCTTCC CGGCTGTCTT ACAGTCCTCA
 601 GGACTCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAGCTTGGG CACCCAGACC
 661 TACATCTGCA ACGTGAATCA CAAGCCCAGC AACACCAAGG TGGACAAGAA AGTTGAGCCC
 721 AAATCTTGTG ACAAAACTCA CACATGCTGT GTCGAGTGTC CACCGTGTCC AGCACCAGAG
 781 GGCGGGCTGA AGATCGCAGC CTTCAACATC CAGACATTTG GGGAGACCAA GATGTCCAAT
 841 GCCACCCTCG TCAGCTACAT TGTGCAGATC CTGAGCCGCT ACGACATCGC CCTGGTCCAG
 901 GAGGTCAGAG ACAGCCACCT GACTGCCGTG GGGAAGCTGC TGGACAACCT CAATCAGGAC
 961 GCACCAGACA CCTATCACTA CGTGGTCAGT GAGCCACTGG GACGGAACAG CTATAAGGAG
 1021 CGCTACCTGT TCGTGACAG GCCTGACCAG GTGTCTGCGG TGGACAGCTA CTACTACGAT
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 1141 TTCTCCCGGT TCACAGAGGT CAGGGAGTTT GCCATTGTTC CCCTGCATGC GGCCCCGGGG
 1201 GACGCAGTAG CCGAGATCGA CGCTCTCTAT GACGTCTACC TGGATGTCCA AGAGAAATGG
 1261 GGCTTGGAGG ACGTCATGTT GATGGGCGAC TTCAATGCGG GCTGCAGCTA TGTGAGACCC
 1321 TCCCAGTGGT CATCCATCCG CCTGTGGACA AGCCCCACCT TCCAGTGGCT GATCCCCGAC
 1381 AGCGCTGACA CCACAGCTAC ACCCAGGCAC TGTGCCTATG ACAGGATCGT GGTTCAGGGG
 1441 ATGCTGCTCC GAGGGGCCGT TGTTCCTGAC TCGGCTCTTC CCTTTAACTT CCAGGCTGCC
 1501 TATGGCCTGA GTGACCAACT GGCCCAAGCC ATCAGTGACC ACTATCCAGT GGAGGTGATG
 1561 CTGAAGGGGG GCGGACCCAA AAAGAAGCGC AAGGTTTGA

//

Fig. 19(C)

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```

          9      18      27      36      45      54
5'  ATG GGA TGG AGC TGT ATC ATC CTC TTC TTG GTA GCA ACA GCT ACA GGT GTC CAC
-----
      M  G  W  S  C  I  I  L  F  L  V  A  T  A  T  G  V  H

          63      72      81      90      99      108
TCC CAG GTG CAG CTG GTG CAG TCT GGG GCA GAG GTG AAA AAG CCT GGG GCC TCA
-----
      S  Q  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  A  S

          117      126      135      144      153      162
GTG AAG GTG TCC TGC AAG GCT TCT GGC TAC ACC TTC AGT GCC TAC TGG ATA GAG
-----
      V  K  V  S  C  K  A  S  G  Y  T  F  S  A  Y  W  I  E

          171      180      189      198      207      216
TGG GTG CGC CAG GCT CCA GGA AAG GGC CTC GAG TGG GTC GGA GAG ATT TTA CCT
-----
      W  V  R  Q  A  P  G  K  G  L  E  W  V  G  E  I  L  P

          225      234      243      252      261      270
GGA AGT AAT AAT TCT AGA TAC AAT GAG AAG TTC AAG GGC CGA GTG ACA GTC ACT
-----
      G  S  N  N  S  R  Y  N  E  K  F  K  G  R  V  T  V  T

          279      288      297      306      315      324
AGA GAC ACA TCC ACA AAC ACA GCC TAC ATG GAG CTC AGC AGC CTG AGG TCT GAG
-----
      R  D  T  S  T  N  T  A  Y  M  E  L  S  S  L  R  S  E

          333      342      351      360      369      378
GAC ACA GCC GTC TAT TAC TGT GCA AGA TCC TAC GAC TTT GCC TGG TTT GCT TAC
-----
      D  T  A  V  Y  Y  C  A  R  S  Y  D  F  A  W  F  A  Y

          387      396      405      414      423      432
TGG GGC CAA GGG ACT CTG GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG
-----
      W  G  Q  G  T  L  V  T  V  S  S  A  S  T  K  G  P  S

          441      450      459      468      477      486
GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT GGG GGC ACA GCG GCC CTG
-----
      V  F  P  L  A  P  S  S  K  S  T  S  G  G  T  A  A  L

          495      504      513      522      531      540
GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TGA
-----
      G  C  L  V  K  D  Y  F  P  E  P  V  T  V  S  W  N  S

          549      558      567      576      585      594
GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA
-----
      G  A  L  T  S  G  V  H  T  F  P  A  V  L  Q  S  S  G

```

Fig. 19(D)
(Sheet 1 of 3)

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603	612	621	630	639	648
CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG					
L Y S L S S V V T V P S S S L G T Q					
657	666	675	684	693	702
ACC TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA					
T Y I C N V N H K P S N T K V D K K					
711	720	729	738	747	756
GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC TGT GTG GAG TGC CCA CCG					
V E P K S C D K T H T C C V E C P P					
765	774	783	792	801	810
TGC CCA GCA CCT GAA GGC GGG CTG AAG ATC GCA GCC TTC AAC ATC CAG ACA TTT					
C P A P E G G L K I A A F N I Q T F					
819	828	837	846	855	864
GGG GAG ACC AAG ATG TCC AAT GCC ACC CTC GTC AGC TAC ATT GTG CAG ATC CTG					
G E T K M S N A T L V S Y I V Q I L					
873	882	891	900	909	918
AGC CGC TAC GAC ATC GCC CTG GTC CAG GAG GTC AGA GAC AGC CAC CTG ACT GCC					
S R Y D I A L V Q E V R D S H L T A					
927	936	945	954	963	972
GTG GGG AAG CTG CTG GAC AAC CTC AAT CAG GAC GCA CCA GAC ACC TAT CAC TAC					
V G K L L D N L N Q D A P D T Y H Y					
981	990	999	1008	1017	1026
GTG GTC AGT GAG CCA CTG GGA CGG AAC AGC TAT AAG GAG CGC TAC CTG TTC GTG					
V V S E P L G R N S Y K E R Y L F V					
1035	1044	1053	1062	1071	1080
TAC AGG CCT GAC CAG GTG TCT GCG GTG GAC AGC TAC TAC TAC GAT GAT GGC TGC					
Y R P D Q V S A V D S Y Y Y D D G C					
1089	1098	1107	1116	1125	1134
GAG CCC TGC GGG AAC GAC ACC TTC AAC CGA GAG CCA GCC ATT GTC AGG TTC TTC					
E P C G N D T F N R E P A I V R F F					
1143	1152	1161	1170	1179	1188
TCC CGG TTC ACA GAG GTC AGG GAG TTT GCC ATT GTT CCC CTG CAT GCG GCC CCG					
S R F T E V R E F A I V P L H A A P					
1197	1206	1215	1224	1233	1242

Fig. 19(D)
(Sheet 2 of 3)

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```

GGG GAC GCA GTA GCC GAG ATC GAC GCT CTC TAT GAC GTC TAC CTG GAT GTC CAA
-----
G   D   A   V   A   E   I   D   A   L   Y   D   V   Y   L   D   V   Q

      1251      1260      1269      1278      1287      1296
GAG AAA TGG GGC TTG GAG GAC GTC ATG TTG ATG GGC GAC TTC AAT GCG GGC TGC
-----
E   K   W   G   L   E   D   V   M   L   M   G   D   F   N   A   G   C

      1305      1314      1323      1332      1341      1350
AGC TAT GTG AGA CCC TCC CAG TGG TCA TCC ATC CGC CTG TGG ACA AGC CCC ACC
-----
S   Y   V   R   P   S   Q   W   S   S   I   R   L   W   T   S   P   T

      1359      1368      1377      1386      1395      1404
TTC CAG TGG CTG ATC CCC GAC AGC GCT GAC ACC ACA GCT ACA CCC ACG CAC TGT
-----
F   Q   W   L   I   P   D   S   A   D   T   T   A   T   P   T   H   C

      1413      1422      1431      1440      1449      1458
GCC TAT GAC AGG ATC GTG GTT GCA GGG ATG CTG CTC CGA GGG GCC GTT GTT CCC
-----
A   Y   D   R   I   V   V   A   G   M   L   L   R   G   A   V   V   P

      1467      1476      1485      1494      1503      1512
GAC TCG GCT CTT CCC TTT AAC TTC CAG GCT GCC TAT GGC CTG AGT GAC CAA CTG
-----
D   S   A   L   P   F   N   F   Q   A   A   Y   G   L   S   D   Q   L

      1521      1530      1539      1548      1557      1566
GCC CAA GCC ATC AGT GAC CAC TAT CCA GTG GAG GTG ATG CTG AAG GGG GGC GGA
-----
A   Q   A   I   S   D   H   Y   P   V   E   V   M   L   K   G   G   G

      1575      1584
CCC AAA AAG AAG CGC AAG GTT TGA 3'
-----
P   K   K   K   R   K   V   *

```

Fig. 19(D)
(Sheet 3 of 3)

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Mammalian expression of humanised HMFG1-D Nase constructs

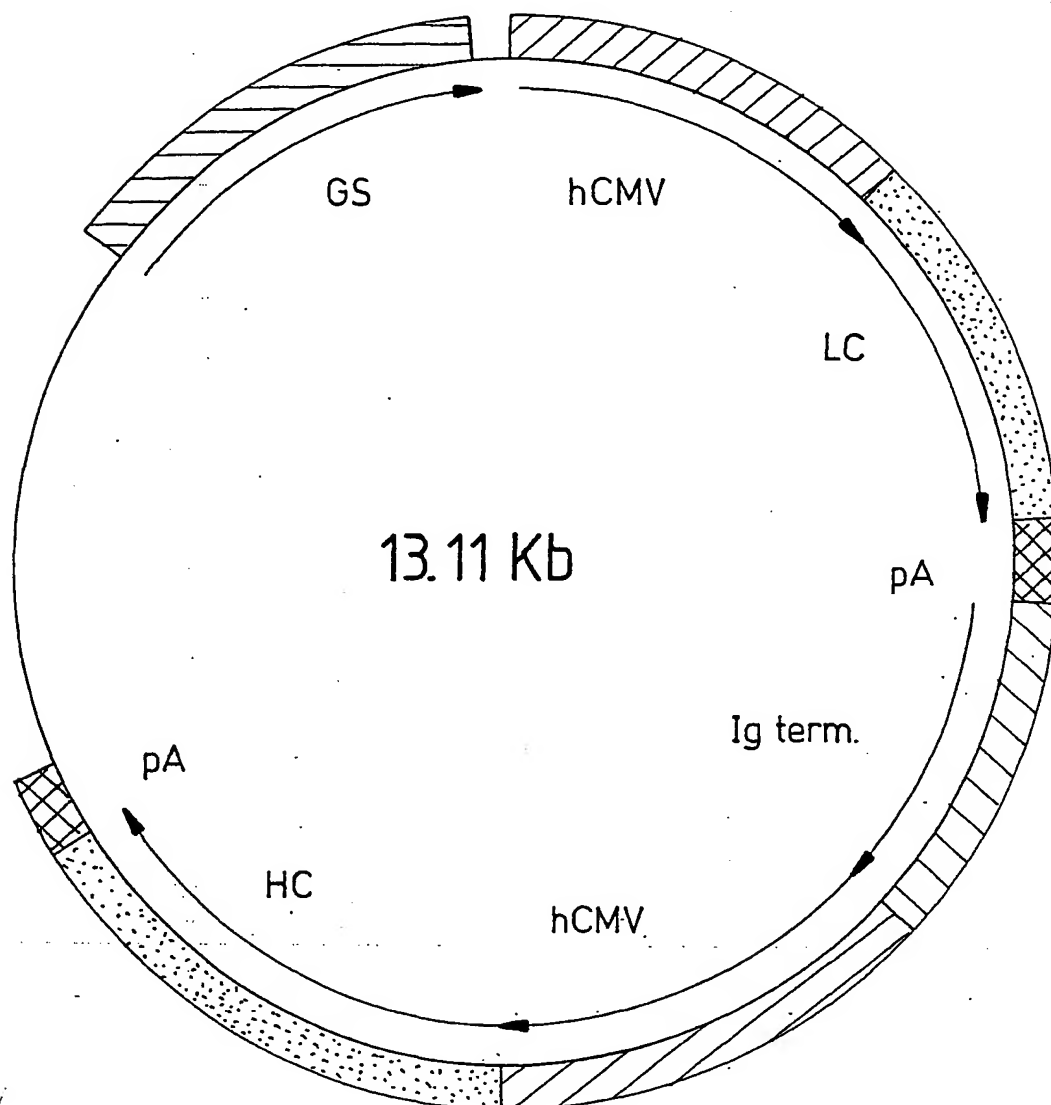
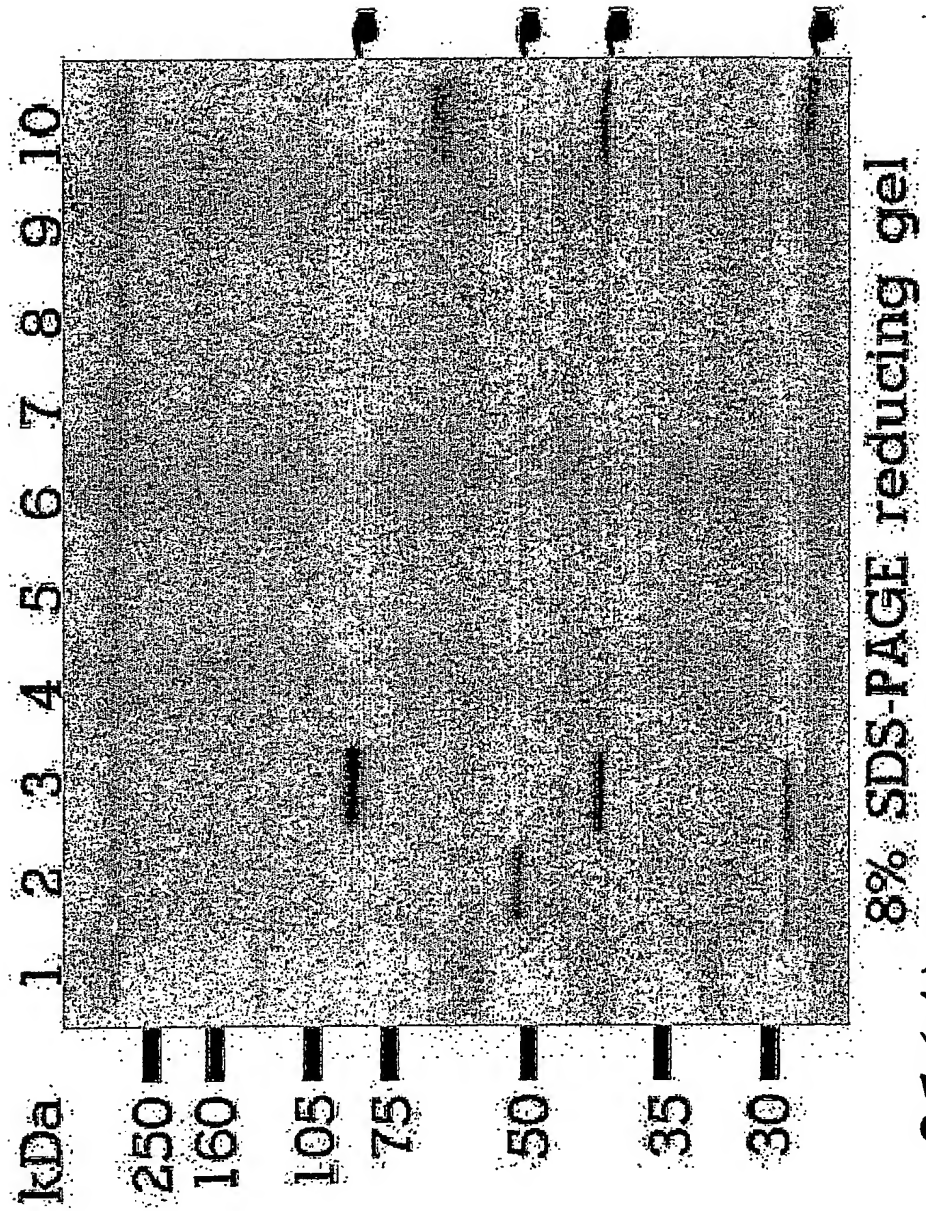


Fig. 20

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Immuno-precipitation of metabolically labelled transient transfectants

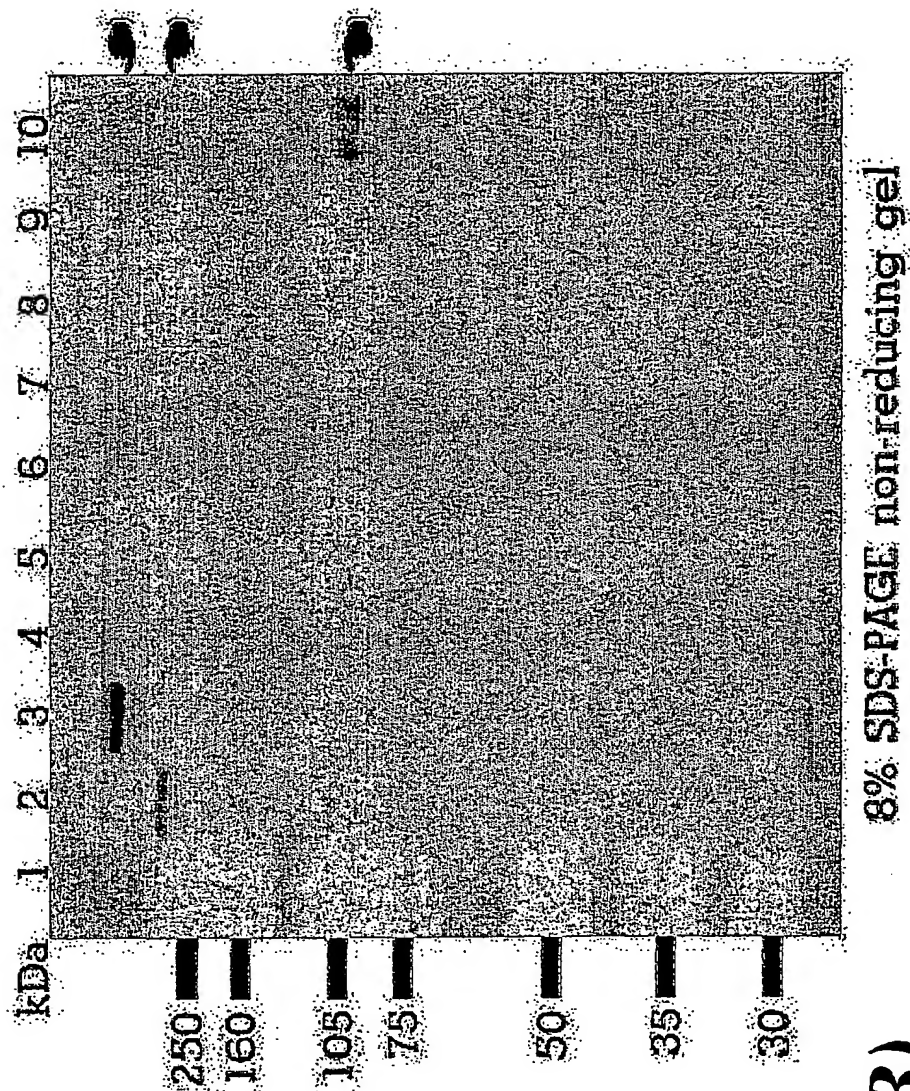


8% SDS-PAGE reducing gel

Fig. 21(A)

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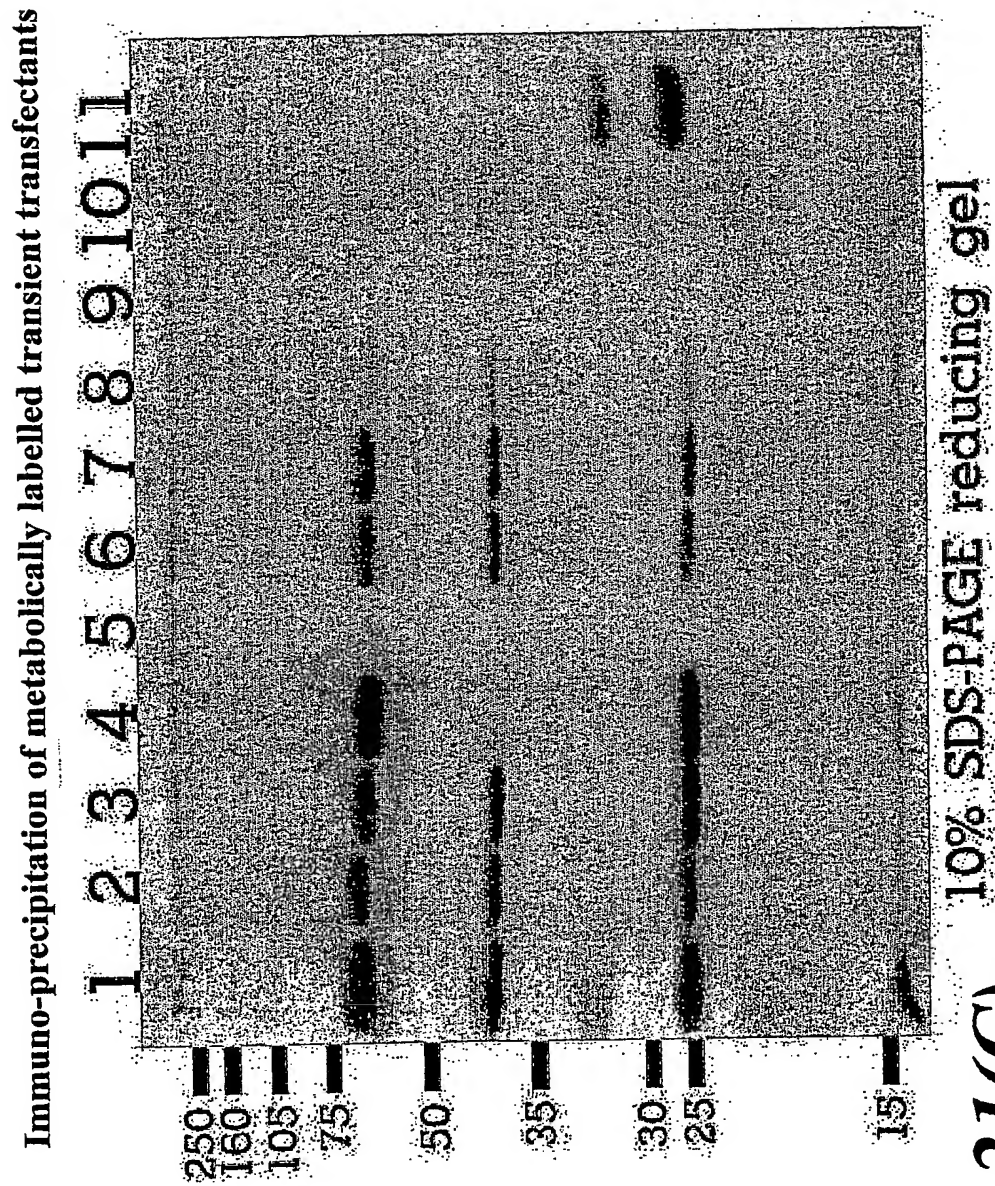
Immuno-precipitation of metabolically labelled transient transfectants



8% SDS-PAGE non-reducing gel

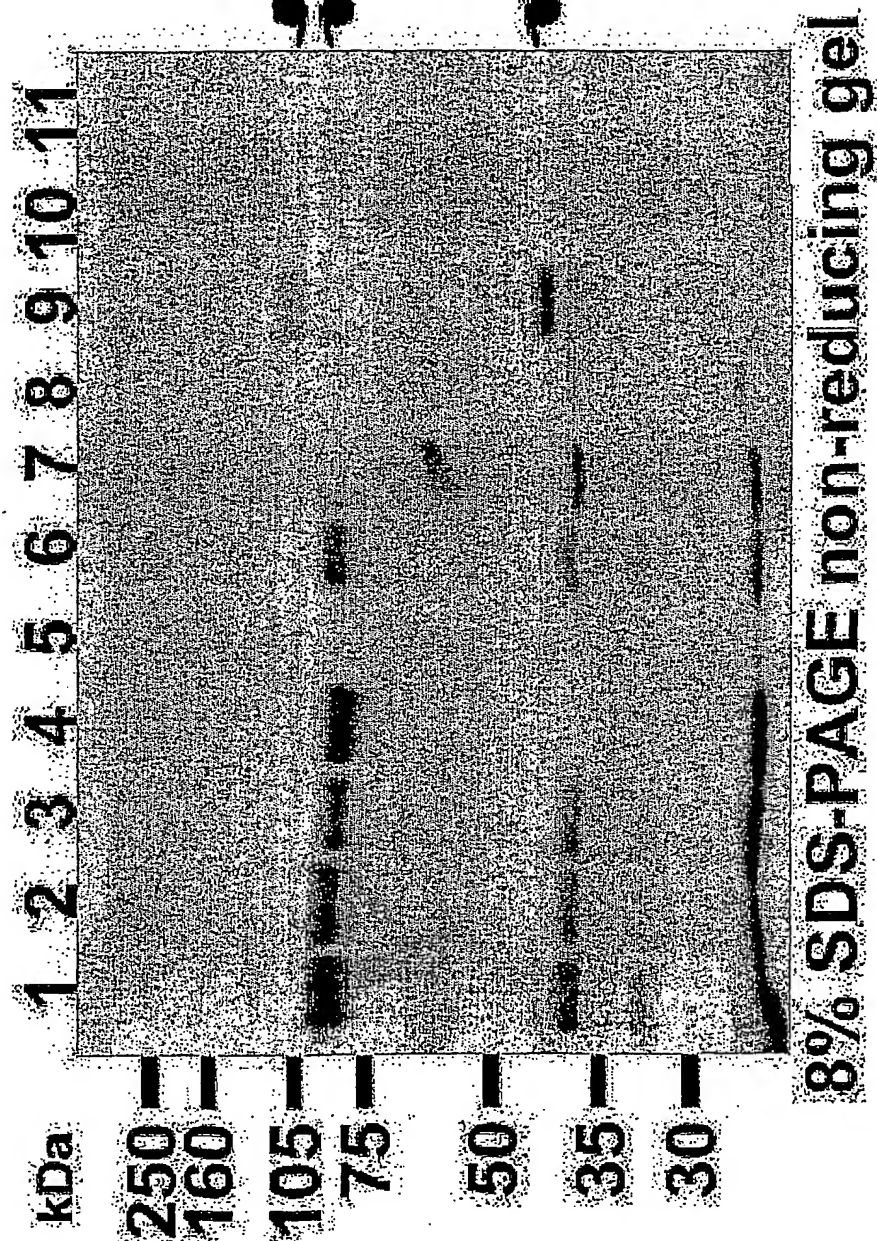
Fig. 21(B)

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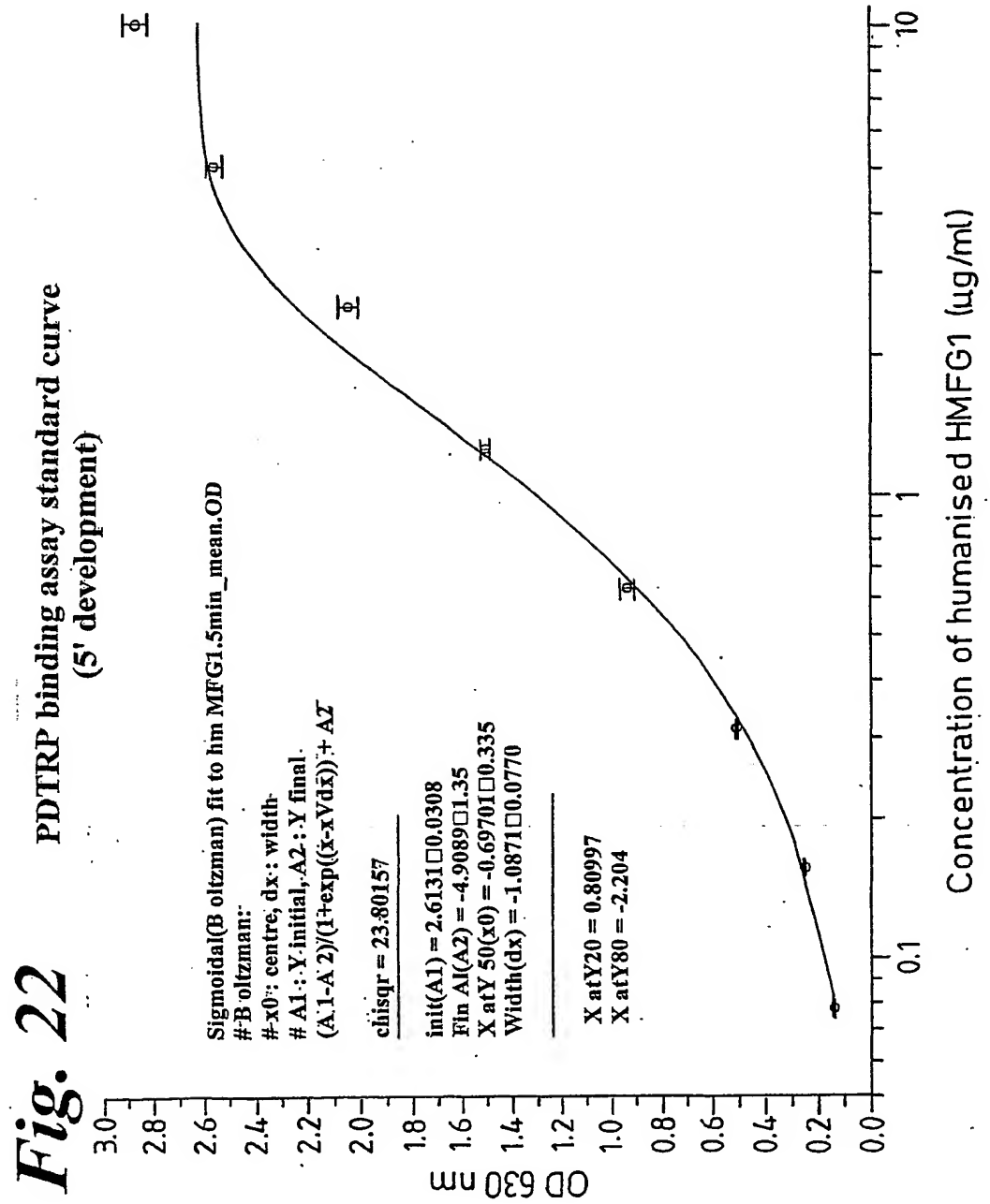
**Fig. 21(C)**

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Immuno-precipitation of metabolically labelled transient transfectants

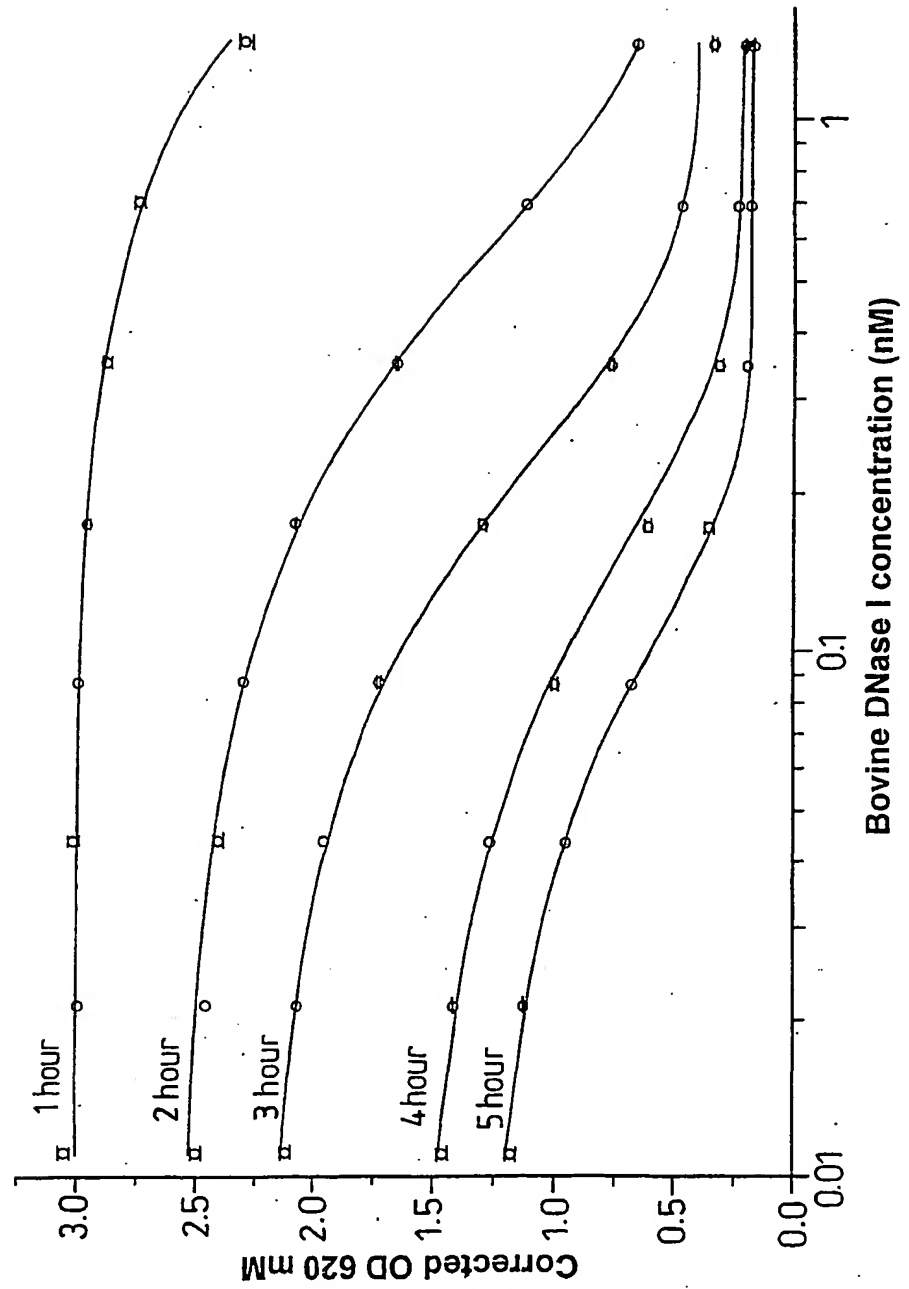
*Fig. 21(D)*

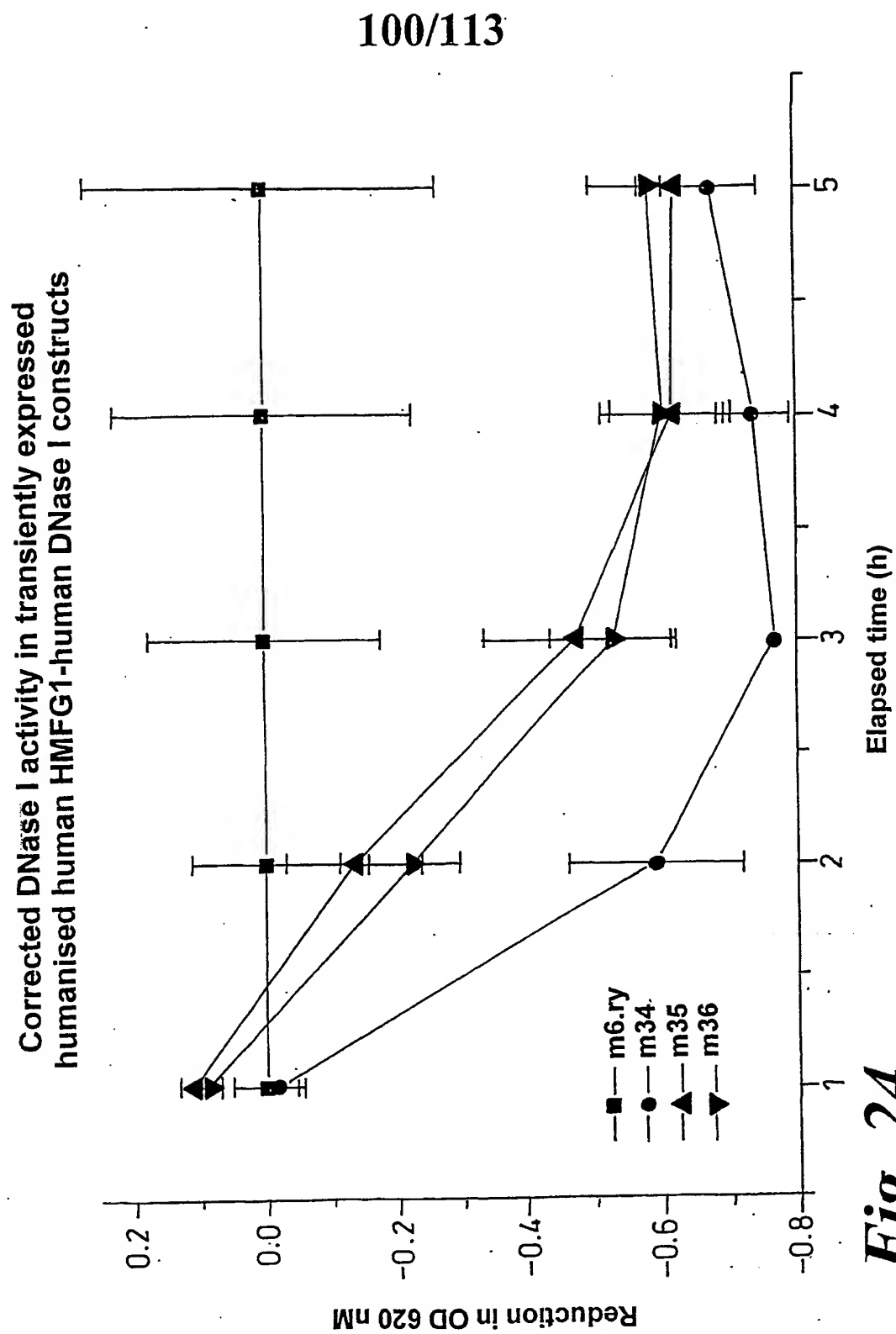
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Fig. 23
Corrected bovine DNase I standard curves
at various time points



**Fig. 24**

Corrected DNase I activity in transiently expressed
humanised HMG1 F(ab')₂-human DNase I fusions

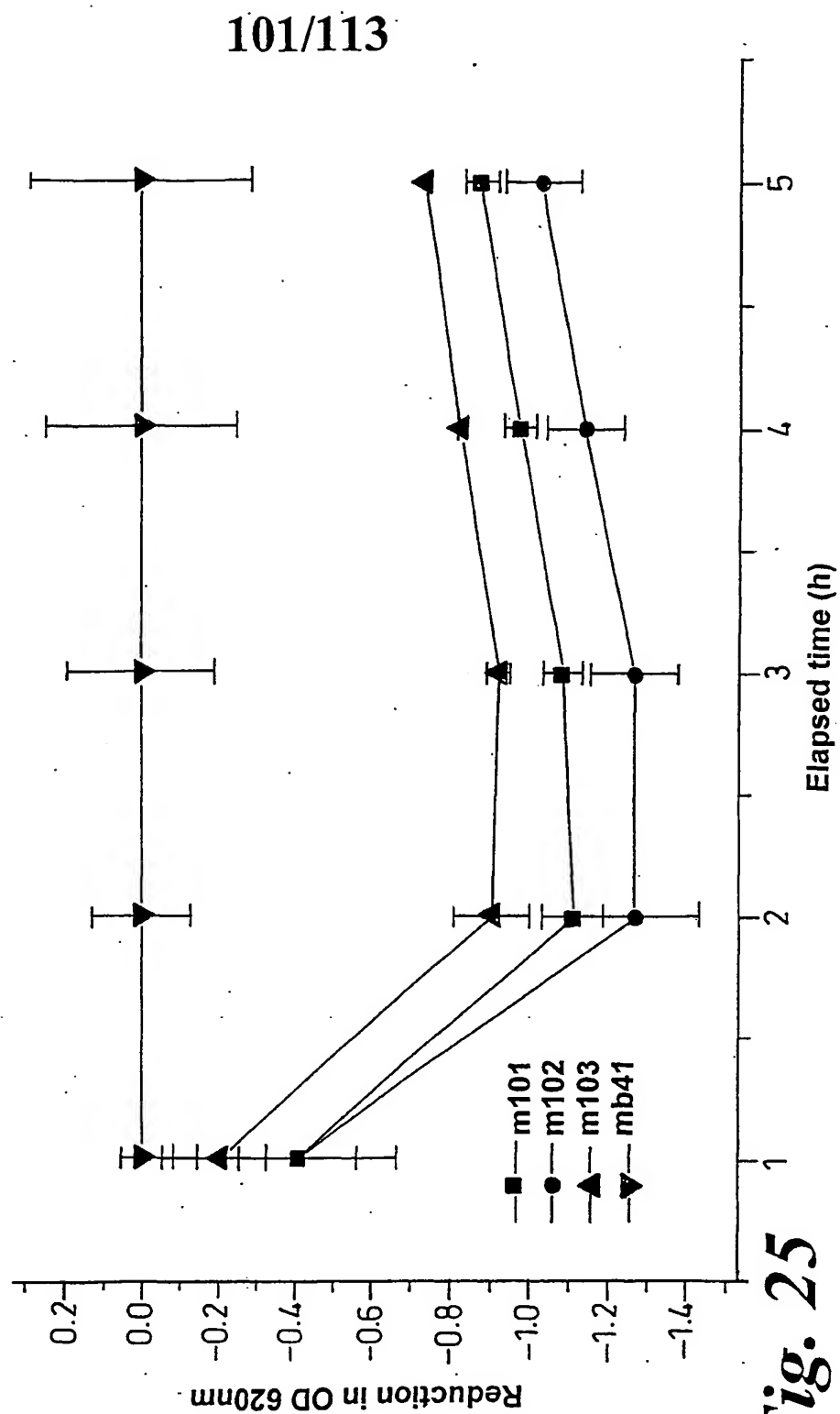
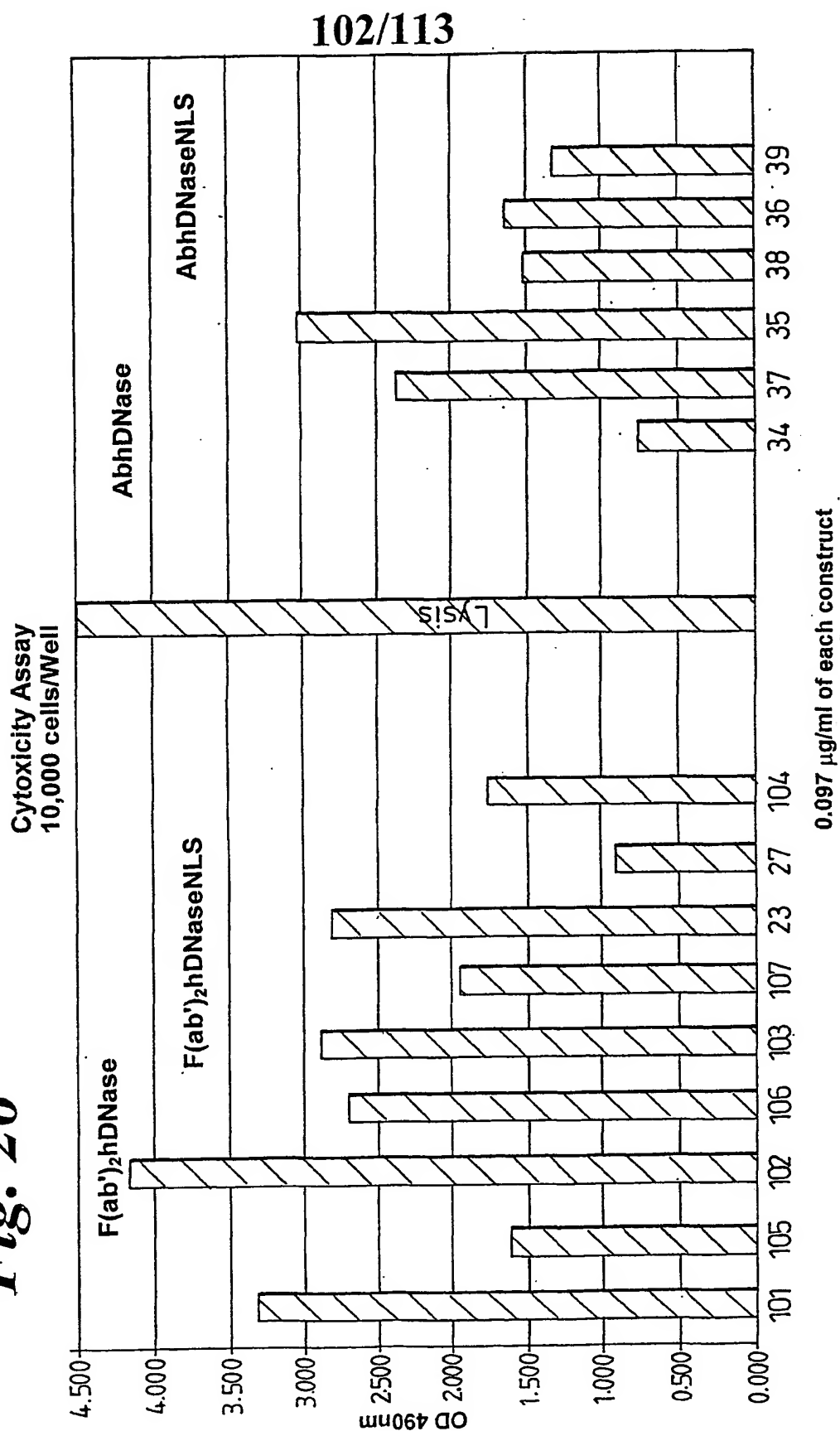


Fig. 25

Fig. 26



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MCF7 cells killed after 1h incubation with 1.35 ng of sample

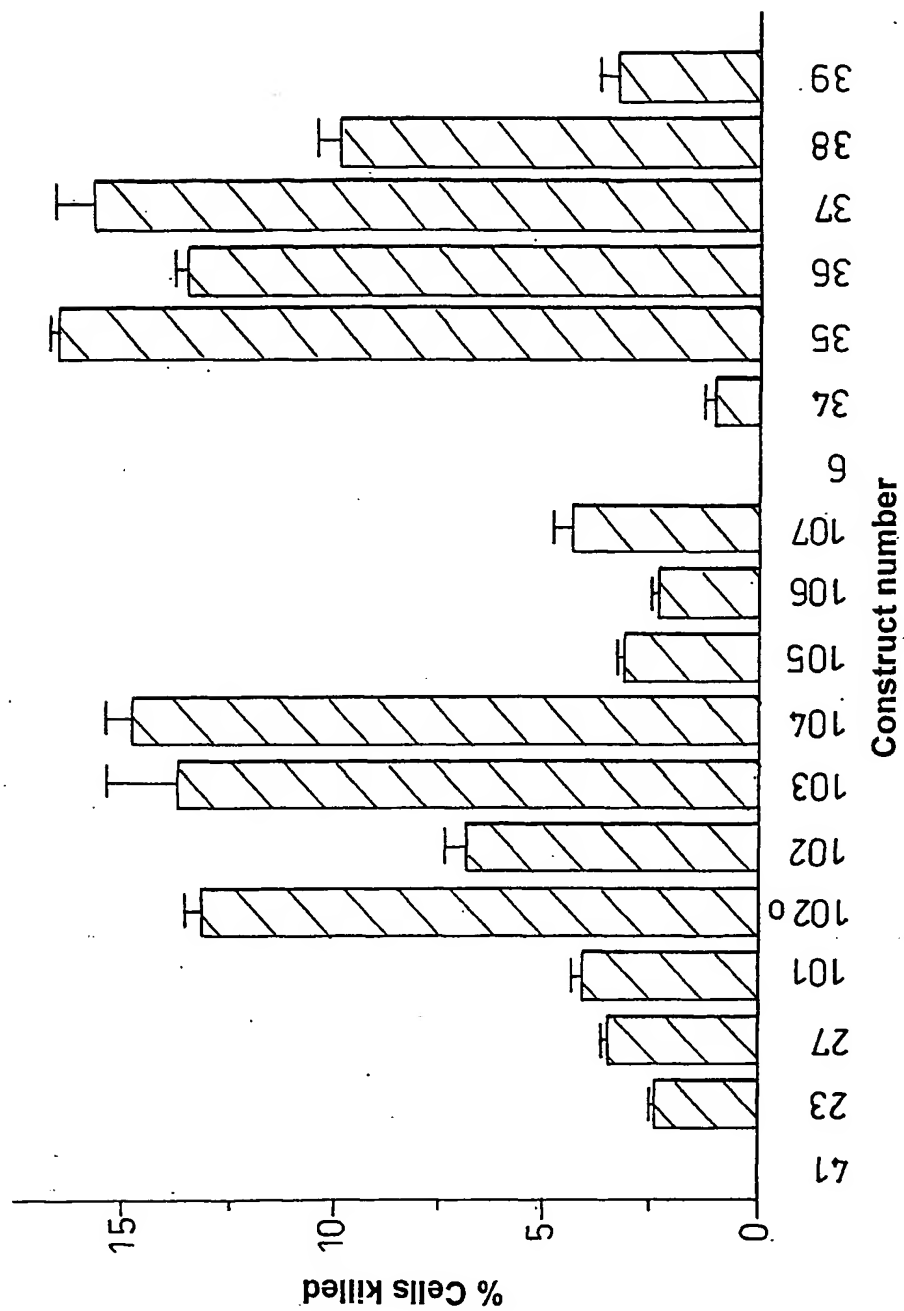
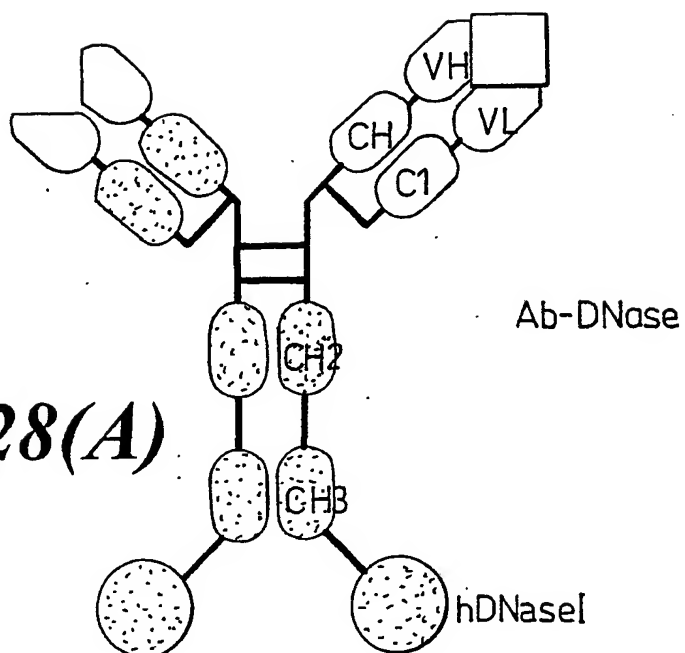
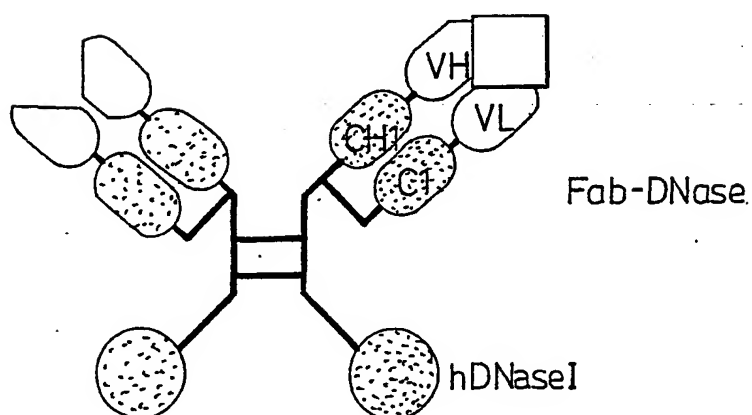
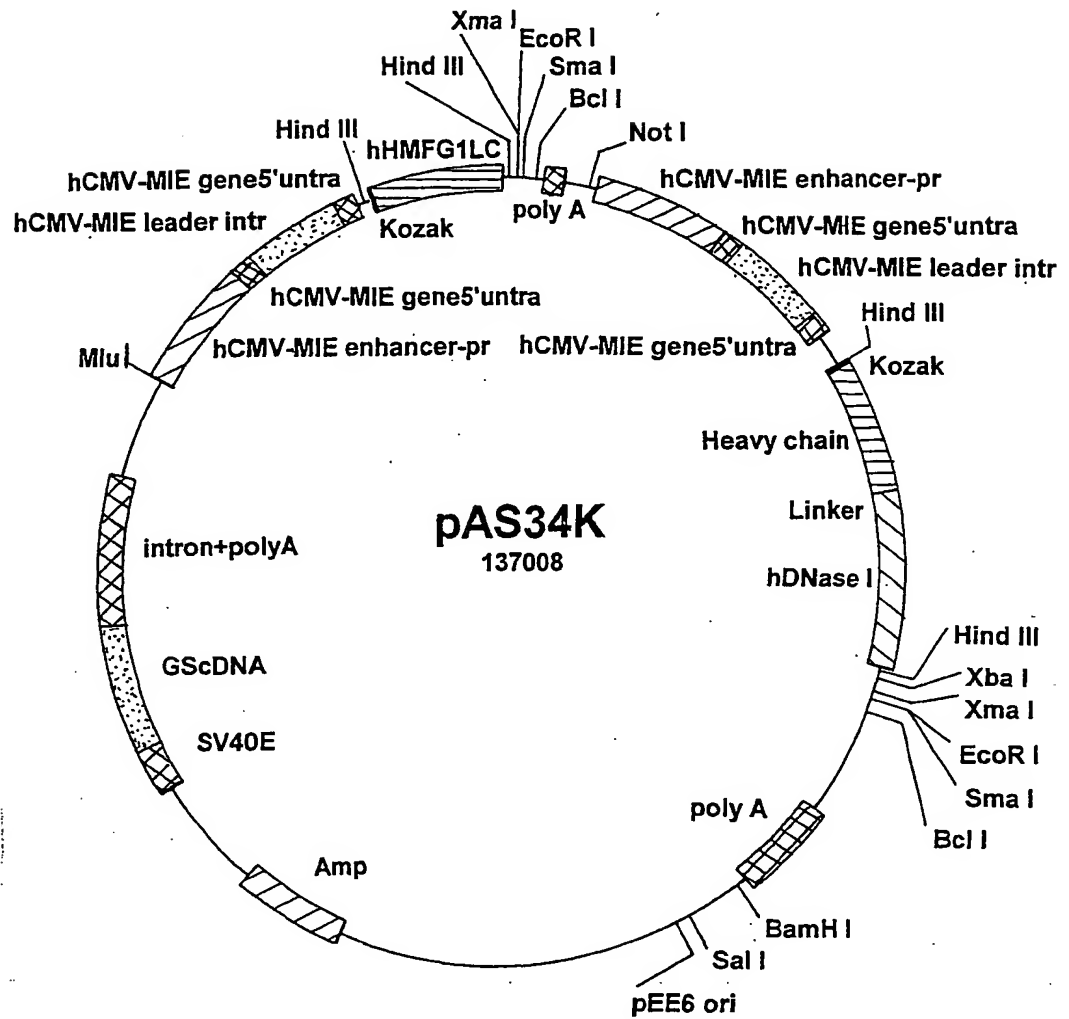


Fig. 27

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Fig. 28(A)**Fig. 28(B)**

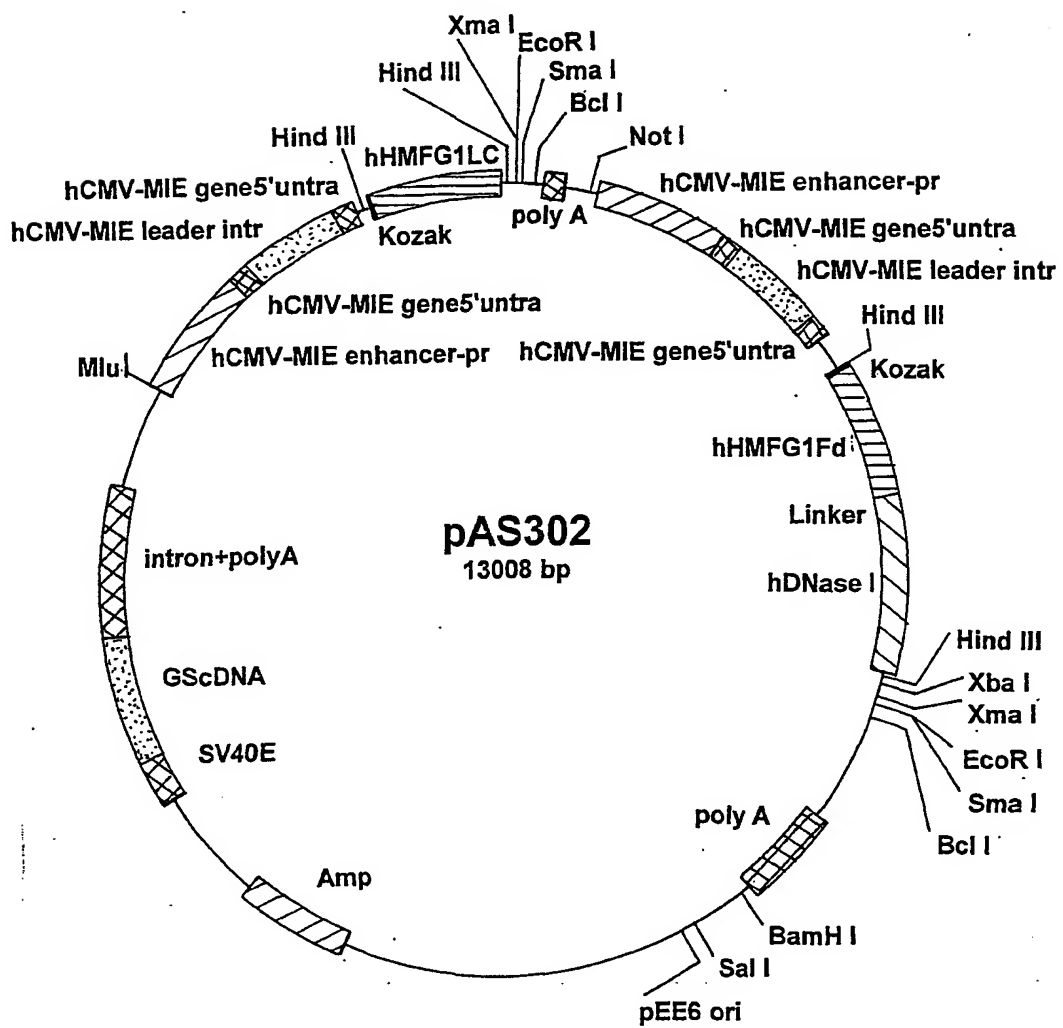
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Ab-DNase

Fig. 29

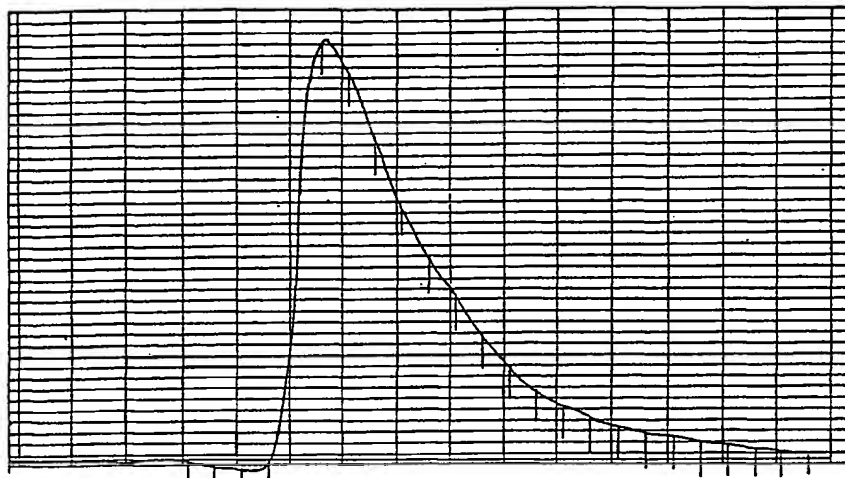
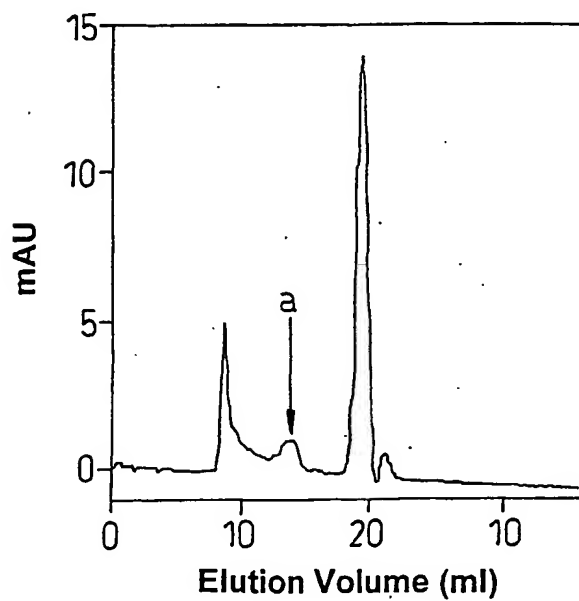
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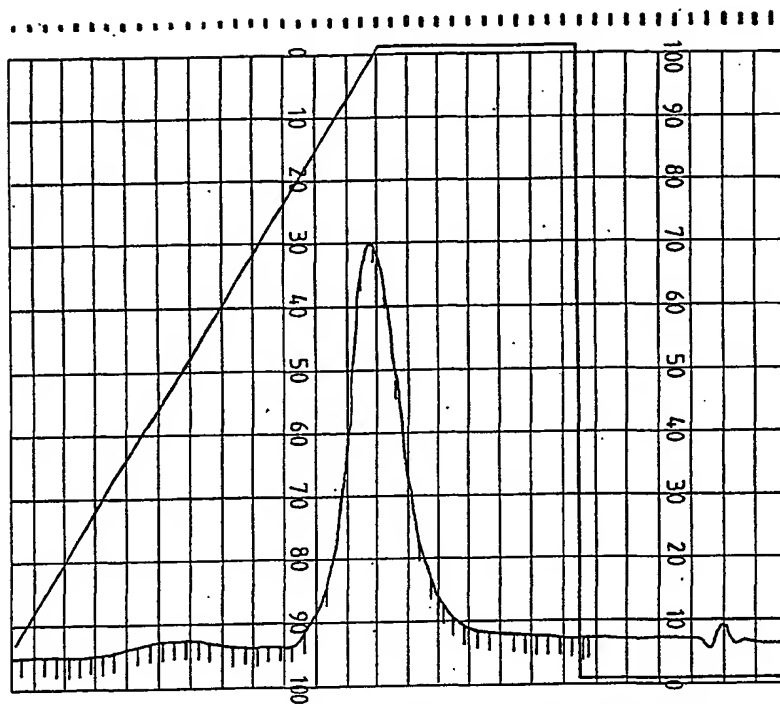
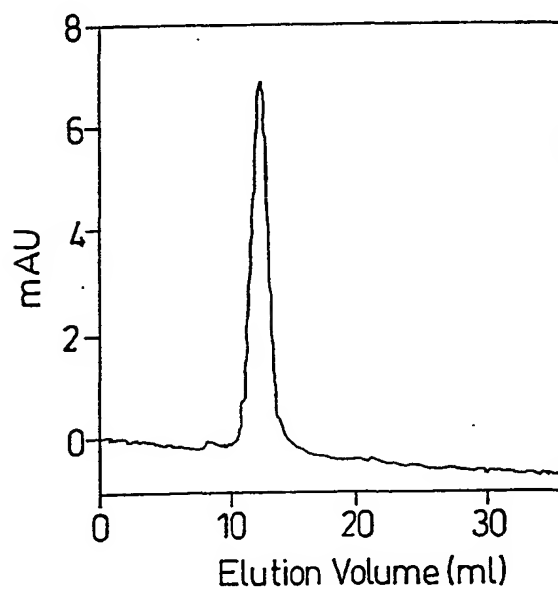
Fab-DNase

Fig. 30

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*Fig. 31(A)**Fig. 31(B)*

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*Fig. 32(A)**Fig. 32(B)*

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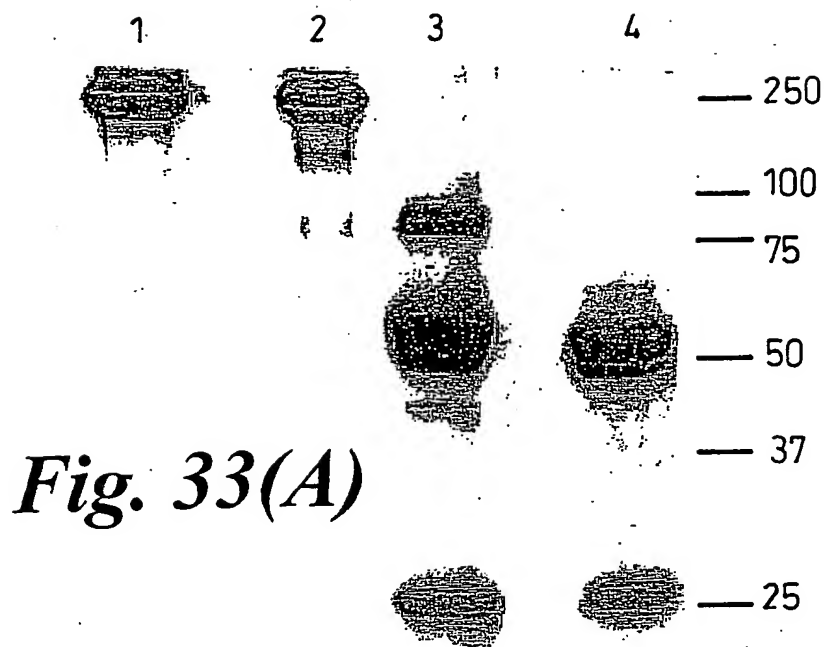


Fig. 33(A)

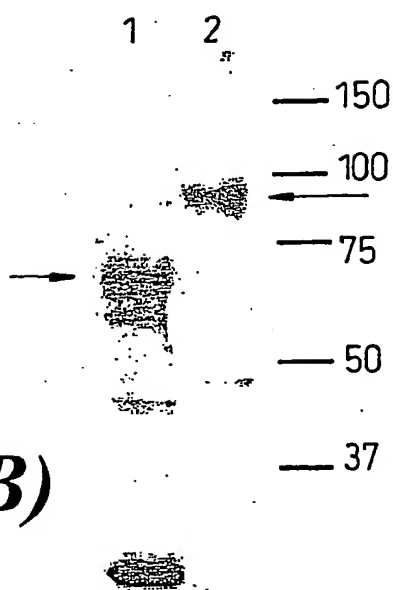
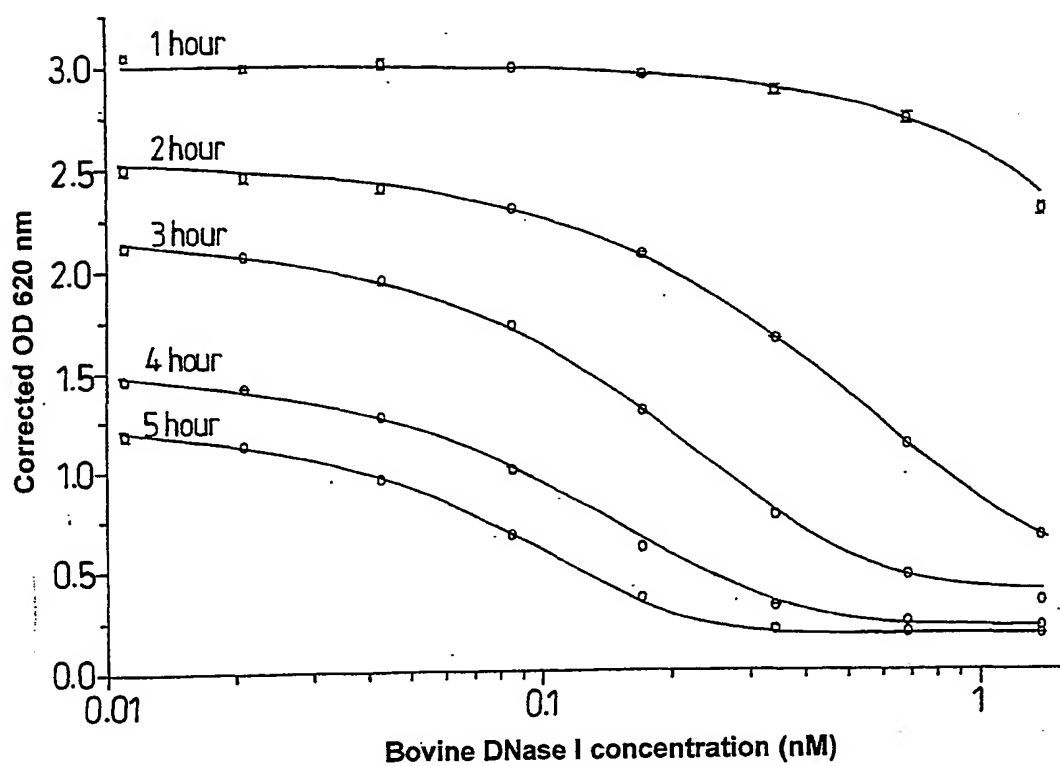
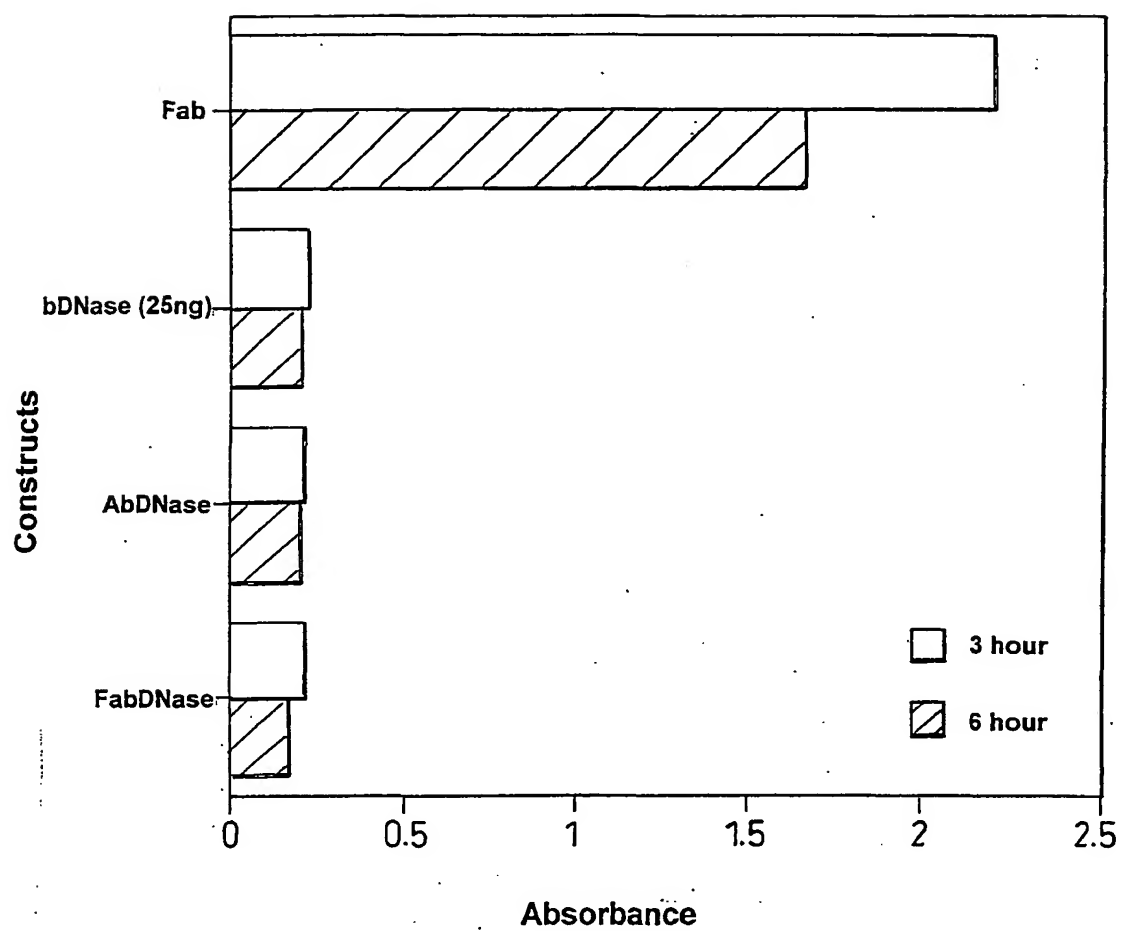


Fig. 33(B)

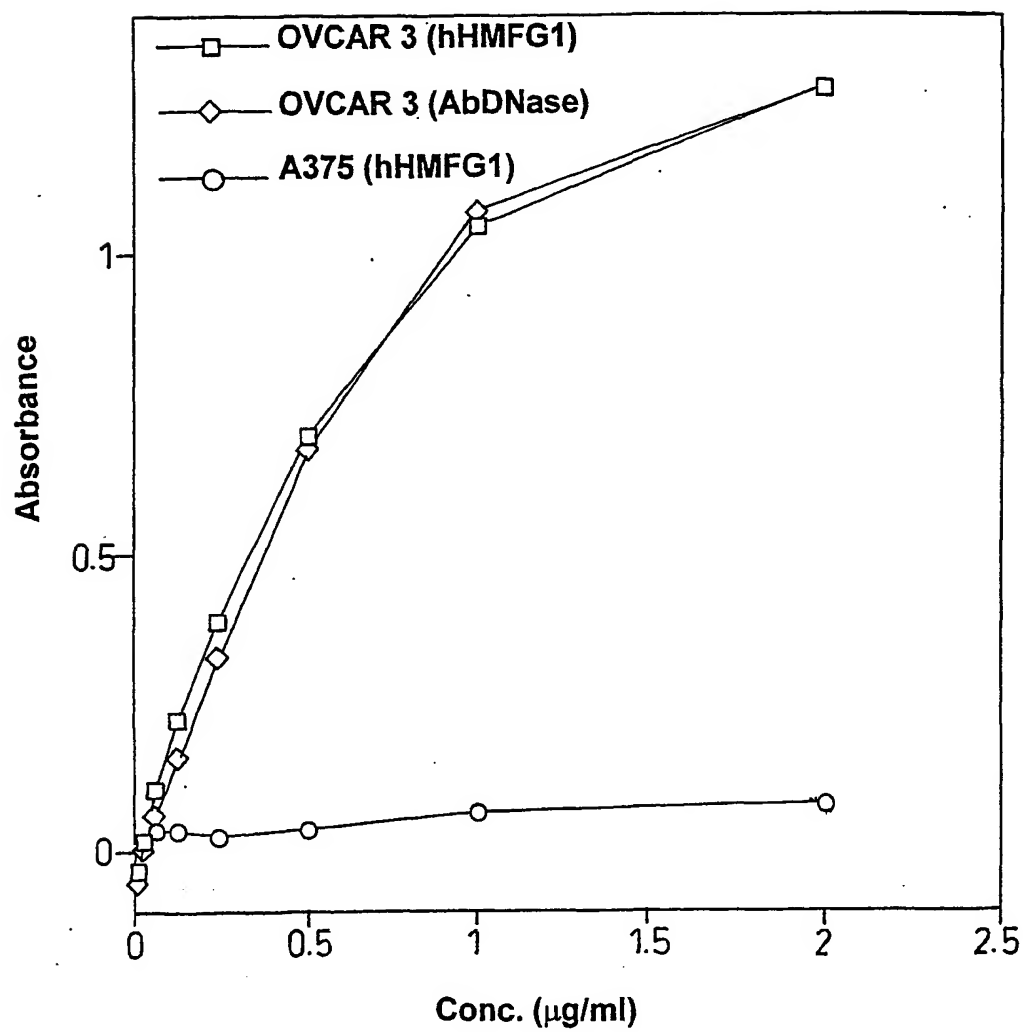
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Bovine DNase I standard curves at various time points***Fig. 34(A)***

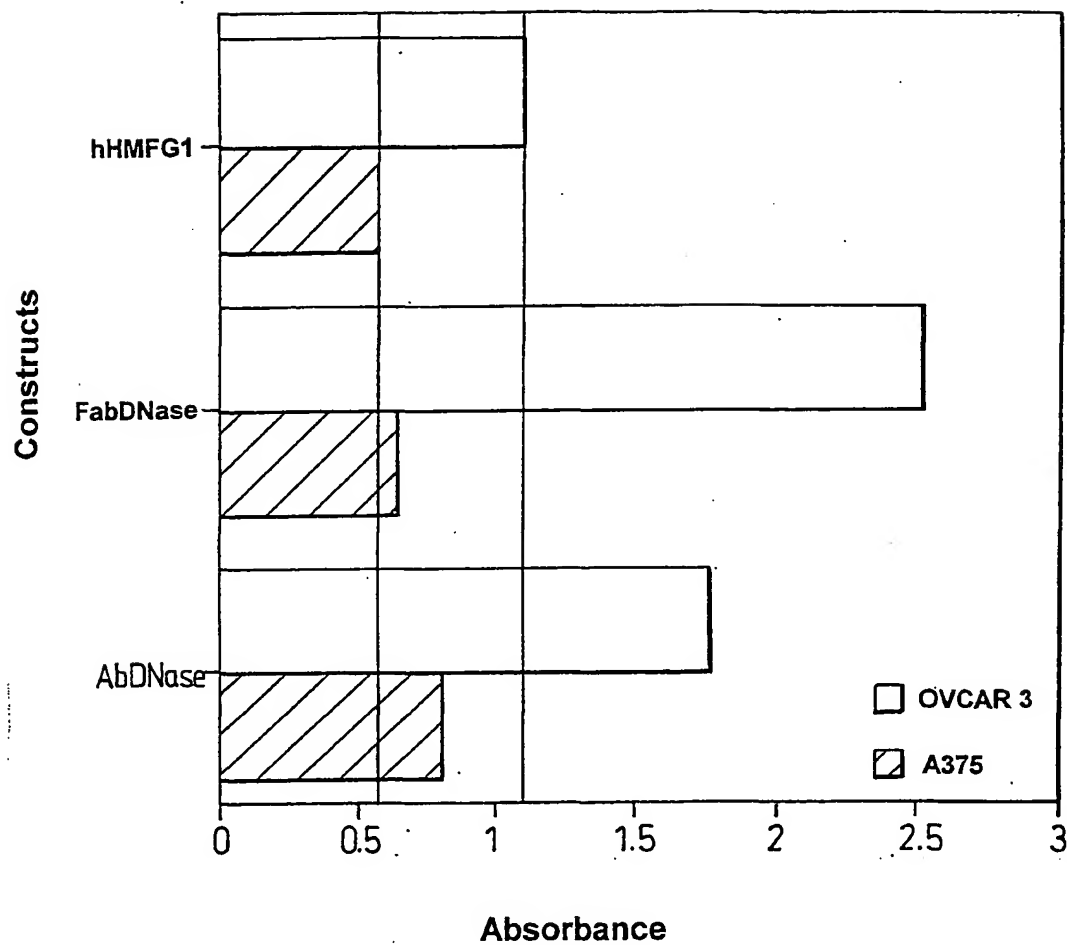
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*Fig. 34(B)*

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*Fig. 35(A)*

113/113

*Fig. 35(B)*

INTERNATIONAL SEARCH REPORT

ational Application No
PCT/GB 01/01324

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K16/18 C12N9/22 C12N15/62 C07K16/46 C12N15/63
C12N15/85 A61K39/395 A61K38/43 //C07K19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, WPI Data, MEDLINE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>YOUNG ROBERT J ET AL: "A DNase I based immunotoxin for tumor therapy." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, no. 41, March 2000 (2000-03), page 289 XP001008862 91st Annual Meeting of the American Association for Cancer Research.; San Francisco, California, USA; April 01-05, 2000, March, 2000 ISSN: 0197-016X abstract</p> <p style="text-align: center;">--- -/-</p>	1-12,14, 15,17, 21,23, 25, 28-35, 37,38

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

6 August 2001

Date of mailing of the international search report

16/08/2001

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Montrone, M

INTERNATIONAL SEARCH REPORT

ational Application No

PCT/GB 01/01324

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 94 15644 A (EPENETOS AGAMEMNON ANTONIOU ;IMP CANCER RES TECH (GB); DEONARAIN M) 21 July 1994 (1994-07-21) abstract page 3, line 12-22 page 4, line 24-26 page 6, line 7 -page 8, line 2 page 10, line 11-14 page 12, line 18 -page 13, line 8 page 15, line 1-19 page 26, line 30 -page 27, line 25 page 28, line 23 -page 29, line 21 page 49, line 29 -page 51, line 10</p>	1-6, 9-19,23, 28-38
Y	<p>LINARDOU H. ET AL.: "Deoxyribonuclease I (DNase I). A novel approach for targeted cancer therapy." CELL BIOPHYS., vol. 24-25, 1994, page 243-248 XP001012902 abstract page 244, paragraphs 2-4 page 245, paragraph 4 page 246; figure 1 page 247, paragraphs 2,3,5</p>	15,16, 18,19
Y	<p>WO 92 04380 A (UNILEVER PLC ;UNILEVER NV (NL)) 19 March 1992 (1992-03-19) cited in the application abstract page 4, line 30 - line 27 page 6, line 6-26 page 8, line 30 -page 9, line 7 page 9, line 11-28 page 10, line 1-6 page 10, line 33 -page 11, line 3 page 12, line 13-35 page 14, line 14-16 page 15, line 15-30 page 16, line 15-20 page 17, line 6-14</p>	1-19,21, 23,25, 27-38
Y	<p>EP. 0 781 845 A (CELLTECH THERAPEUTICS LTD) 2 July 1997 (1997-07-02) abstract page 3, line 19-48 page 5, line 3 -page 6, line 15 page 9, line 23-42 page 16, line 8-17</p>	1-19,21, 23,25, 27-38

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 20,22,24,26,38

Present claims 20, 24 and 38 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Moreover, a search for the subject-matter of claims 22 and 26 has not been carried out since it was not possible to identify the corresponding SEQ.ID.NO. of fig. 14(c). Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely 1 to 19, 21, 23, 25, 27 to 37.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 01/01324

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9415644 A	21-07-1994	AT 164314 T	15-04-1998
		DE 69409225 D	30-04-1998
		DE 69409225 T	13-08-1998
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